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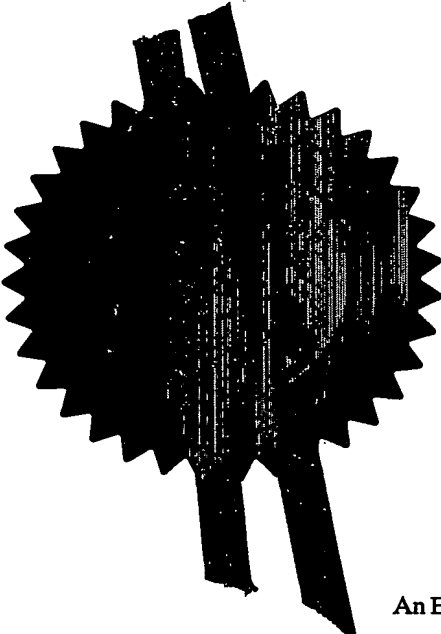
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Dated

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1. Your reference

PA 523

2. Patent application number

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01 OCT 2002

3. Full name, address and postcode of the or of each applicant (underline all surnames)

CELLTECH R & D LIMITED
208 BATH ROAD
SLOUGH
SL1 3WE

Patents ADP number (if you know it)

If the applicant is a corporate body, give the country/state of its incorporation

UK

8121485001

4. Title of the invention

CHEMICAL COMPOUNDS

5. Name of your agent (if you have one)

"Address for service" in the United Kingdom to which all correspondence should be sent (including the postcode)

CELLTECH R & D LIMITED
PATENTS DEPARTMENT
208 BATH ROAD
SLOUGH
SL1 3WE

Patents ADP number (if you know it)

8182305001

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Country

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Date of filing
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7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application

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- a) any applicant named in part 3 is not an inventor, or
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Description

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Priority documents

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Statement of inventorship and right to grant of a patent (Patents Form 7/77)

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11.

I/We request the grant of a patent on the basis of this application.
FOR & ON BEHALF OF CELTECH LTD LIMITED

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Date

30th September 2002

12. Name and daytime telephone number of person to contact in the United Kingdom

Dr P. Ansell 01753 447566

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CHEMICAL COMPOUNDS

5 This invention relates to a series of 5-6 fused ring bicyclic heteroaromatic derivatives, to compositions containing them, to processes for their preparation and to their use in medicine.

10 Immune and inflammatory responses involve a variety of cell types with control and co-ordination of the various interactions occurring *via* both cell-cell contacts (e.g integrin interactions with their receptors) and by way of intercellular signalling molecules. A large number of different signalling molecules are involved including cytokines, lymphocytes, chemokines and growth factors.

15 Cells respond to such intercellular signalling molecules by means of intracellular signalling mechanisms that include protein kinases, phosphatases and phospholipases. There are five classes of protein kinase of which the major ones are the tyrosine kinases and the serine/threonine kinases [Hunter, T., Methods in Enzymology (Protein Kinase Classification)
20 p. 3, Hunter, T. and Sefton, B.M.; eds. Vol. 200, Academic Press; San Diego, 1991].

One sub-class of serine/threonine kinases is the mitogen activating protein (MAP) kinases of which there are at least three families which differ in the
25 sequence and size of the activation loop [Adams, J. L. *et al*, Progress in Medicinal Chemistry p. 1-60, King, F. D. and Oxford, A. W.; eds. vol 38, Elsevier Science, 2001]: the extracellular regulated kinases (ERKs), the c-Jun NH₂ terminal kinases or stress activated kinases (JNKs or SAP kinases) and the p38 kinases which have a threonine-glycine-tyrosine (TGY)
30 activation motif. Both the JNKs and p38 MAP kinases are primarily activated by stress stimuli including, but not limited to, proinflammatory cytokines e.g. tumour necrosis factor (TNF) and interleukin-1 (IL-1), ultraviolet light, endotoxin and chemical or osmotic shock.

Four isoforms of p38 have been described (p38 α / β / γ / δ). The human p38 α enzyme was initially identified as a target of cytokine-suppressive anti-inflammatory drugs (CSAIDs) and the two isoenzymes found were initially
5 termed CSAID binding protein-1 (CSBP-1) and CSBP-2 [Lee, J. C. *et al*, Nature (London) 1994, 372, 739-46]. CSBP-2 is now widely referred to as p38 α and differs from CSBP-1 in an internal sequence of 25 amino acids as a result of differential splicing of two exons that are conserved in both mouse and human [McDonnell, P. C. *et al*, Genomics 1995, 29, 301-2]. CSBP-1 and
10 p38 α are expressed ubiquitously and there is no difference between the two isoforms with respect to tissue distribution, activation profile, substrate preference or CSAID binding. A second isoform is p38 β which has 70% identity with p38 α . A second form of p38 β termed p38 β 2 is also known and of the two this is believed to be the major form. p38 α and p38 β 2 are expressed
15 in many different tissues. However in monocytes and macrophages p38 α is the predominant kinase activity [Lee, J. C., *ibid*; Jing, Y. *et al*, J. Biol. Chem. 1996, 271, 10531-34; Hale, K. K. *et al*, J. Immun. 1999, 162, 4246-52]. p38 γ and p38 δ (also termed SAP kinase-3 and SAP kinase-4 respectively) have ~63% and ~61% homology to p38 α respectively. p38 γ is predominantly
20 expressed in skeletal muscle whilst p38 δ is found in testes, pancreas, prostate, small intestine and in certain endocrine tissues.

All p38 homologues and splice variants contain a 12 amino acid activation loop that includes a Thr-Gly-Tyr motif. Dual phosphorylation of both Thr-180
25 and Tyr-182 in the TGY motif by a dual specificity upstream kinase is essential for the activation of p38 and results in a >1000-fold increase in specific activity of these enzymes [Doza, Y. N. *et al* FEBS Lett., 1995, 364, 7095-8012]. This dual phosphorylation is effected by MKK6 and under certain conditions the related enzyme MKK3 [Enslen, H. *et al* J. Biol. Chem., 1998,
30 273, 1741-48]. MKK3 and MKK6 belong to a family of enzymes termed

MAPKK (mitogen activating protein kinase kinase) which are in turn activated by MAPKKK (mitogen activating kinase kinase kinase) otherwise known as MAP3K.

- 5 Several MAP3Ks have been identified that are activated by a wide variety of stimuli including environmental stress, inflammatory cytokines and other factors. MEKK4/MTK1 (MAP or ERK kinase kinase/MAP three kinase-1), ASK1 (apoptosis stimulated kinase) and TAK1 (TGF- β -activated kinase) are some of the enzymes identified as upstream activators of for MAPKKs.
- 10 MEKK4/MTK1 is thought to be activated by several GADD-45-like genes that are induced in response to environmental stimuli and which eventually lead to p38 activation [Takekawa, M. and Saito, H. Cell, 1998, 95, 521-30]. TAK1 has been shown to activate MKK6 in response to transforming growth factor- β (TGF- β). TNF-stimulated activation of p38 is believed to be mediated by the
- 15 recruitment of TRAF2 [TNF receptor associated factor] and the Fas adaptor protein, Daxx, which results in the activation of ASK1 and subsequently p38.

Several substrates of p38 have been identified including other kinases [e.g. MAPK activated protein kinase 2/3/5 (MAPKAP 2/3/5), p38

20 regulated/activated protein kinase (PRAK), MAP kinase-interacting kinase 1/2 (MNK1/2), mitogen- and stress-activated protein kinase 1 (MSK1/RLPK) and ribosomal S6 kinase-B (RSK-B)], transcription factors [e.g. activating transcription factor 2/6 (ATF2/6), monocyte-enhancer factor-2A/C (MEF2A/C), C/EBP homologous protein (CHOP), Elk1 and Sap-1a1] and

25 others substrates [e.g. cPLA2, p47phox].

MAPKAP K2 is activated by p38 in response to environmental stress. Mice engineered to lack MAPKAP K2 do not produce TNF in response to lipopolysaccharide (LPS). Production of several other cytokines such as IL-1,

30 IL-6, IFN- γ and IL-10 is also partially inhibited [Kotlyarov, A. *et al* Nature Cell Biol. 1999, 1, 94-7]. Further, MAPKAP K2 from embryonic stem cells from

p38 α null mice was not activated in response to stress and these cells did not produce IL-6 in response to IL-1 [Allen, M. *et al*, J. Exp. Med. 2000, 191, 859-69]. These results indicate that MAPKAP K2 is not only essential for TNF and IL-1 production but also for signalling induced by cytokines. In addition
5 MAPKAP K2/3 phosphorylate and thus regulate heat shock proteins HSP 25 and HSP 27 which are involved in cytoskeletal reorganization.

Several small molecule inhibitors of p38 have been reported which inhibit IL-1 and TNF synthesis in human monocytes at concentrations in the low μ M
10 range [Lee, J. C. *et al*, Int. J. Immunopharm. 1988, 10, 835] and exhibit activity in animal models which are refractory to cyclooxygenase inhibitors [Lee, J. C. *et al*, Annals N. Y. Acad. Sci. 1993, 696, 149]. In addition these small molecule inhibitors are known to also decrease the synthesis of a wide variety of pro-inflammatory proteins including IL-6, IL-8,
15 granulocyte/macrophage colony-stimulating factor (GM-CSF) and cyclooxygenase-2 (COX-2). TNF-induced phosphorylation and activation of cytosolic PLA2, TNF-induced expression of VCAM-1 on endothelial cells and IL-1 stimulated synthesis of collagenase and stromelysin are also inhibited by such small molecule inhibitors of p38 [Cohen, P. Trends Cell Biol. 1997, 7,
20 353-61].

A variety of cells including monocytes and macrophages produce TNF and IL-1. Excessive or unregulated TNF production is implicated in a number of disease states including Crohn's disease, ulcerative colitis, pyresis,
25 rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions, toxic shock syndrome, endotoxic shock, sepsis, septic shock, gram negative sepsis, bone resorption diseases, reperfusion injury, graft vs. host reaction, allograft rejection, adult respiratory distress syndrome, chronic pulmonary inflammatory disease, silicosis, pulmonary
30 sarcoisosis, cerebral malaria, scar tissue formation, keloid formation, fever and myalgias due to infection, such as influenza, cachexia secondary to

acquired immune deficiency syndrome (AIDS), cachexia secondary to infection or malignancy, AIDS or AIDS related complex.

5 Excessive or unregulated IL-1 production has been implicated in rheumatoid arthritis, osteoarthritis, traumatic arthritis, rubella arthritis, acute synovitis, psoriatic arthritis, cachexia, Reiter's syndrome, endotoxemia, toxic shock syndrome, tuberculosis, atherosclerosis, muscle degeneration, and other acute or chronic inflammatory diseases such as the inflammatory reaction induced by endotoxin or inflammatory bowel disease. In addition IL-1 has
10 been linked to diabetes and pancreatic β cells [Dinarello, C. A. J. Clinical Immunology, 1985, 5, 287-97].

IL-8 is a chemotactic factor produced by various cell types including endothelial cells, mononuclear cells, fibroblasts and keratinocytes. IL-1, TNF
15 and LPS all induce the production of IL-8 by endothelial cells. *In vitro* IL-8 has been shown to have a number of functions including being a chemoattractant for neutrophils, T-lymphocytes and basophils. IL-8 has also been shown to increase the surface expression of Mac-1 (CD11b/CD18) on neutrophils without *de novo* protein synthesis which may contribute to increased
20 adhesion of neutrophils to vascular endothelial cells. Many diseases are characterised by massive neutrophil infiltration. Histamine release from basophils (in both atopic and normal individuals) is induced by IL-8 as is lysozomal enzyme release and respiratory burst from neutrophils.

25 The central role of IL-1 and TNF together with other leukocyte derived cytokines as important and critical inflammatory mediators is well documented. The inhibition of these cytokines has been shown or would be expected to be of benefit in controlling, alleviating or reducing many of these disease states.

The central position that p38 occupies within the cascade of signalling molecules mediating extracellular to intracellular signalling and its influence over not only IL-1, TNF and IL-8 production but also the synthesis and/or action of other pro-inflammatory proteins (e.g. IL-6, GM-CSF, COX-2, collagenase and stromelysin) make it an attractive target for inhibition by small molecule inhibitors with the expectation that such inhibition would be a highly effective mechanism for regulating the excessive and destructive activation of the immune system. Such an expectation is supported by the potent and diverse anti-inflammatory activities described for p38 kinase inhibitors [Adams, *ibid*; Badger, *et al*, J. Pharm. Exp. Ther. 1996, 279, 1453-61; Griswold, *et al*, Pharmacol. Comm., 1996, 7, 323-29].

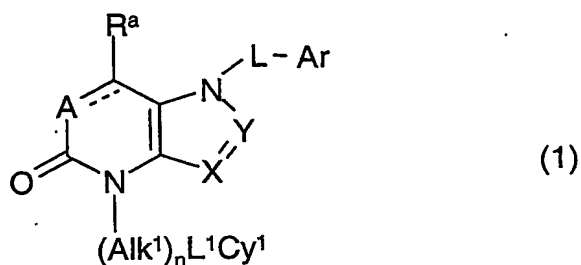
Certain *N,N'*-dibenzylated 2-purinones have been described (Andresen, *et al*, Tetrahedron, 52, 12979-12992).

15

We have now found a group of compounds which are potent and selective inhibitors of p38 kinase (p38 α , β , δ and γ) and the isoforms and splice variants thereof, especially p38 α , p38 β and p38 β 2. The compounds are thus of use in medicine, for example in the prophylaxis and treatment of immune or inflammatory disorders as described herein.

20

Thus according to one aspect of the invention we provide a compound of formula (1):



5

wherein:

the dashed line joining A and C(R^a) is present and represents a bond and A is a -N= atom or a -C(R^b)= group, or the dashed line is absent and A is a

10 -C(R^b)(R^c)- or -N(R^d)- group;

R^a, R^b and R^c is each independently a hydrogen or halogen atom or an optionally substituted alkyl, -CN, -CO₂R¹ (where R¹ is a hydrogen atom or an optionally substituted alkyl group) or -CONR¹R² group (where R² is a hydrogen atom or an optionally substituted alkyl group);

15 R^d is a hydrogen atom or an alkyl group;

X and Y is each a nitrogen atom or a -C(R^e)= or -C(Alk²R^e)= group [where Alk² is an optionally substituted alkylene, alkenylene or alkynylene chain and R^e is a hydrogen or halogen atom or a -CN, -OR¹, -CO₂R¹, -C(X^a)R¹ (where X^a is an oxygen or sulphur atom), -Cy² (where Cy² is an optionally substituted,

20 saturated or unsaturated non-aromatic carbocyclic ring optionally containing one or more -O-, -S-, -NH- or -C(X^a)- atoms or groups), -NR^{1a}R^{2a} (where R^{1a} and R^{2a}, which may be the same or different, is each a hydrogen atom or an optionally substituted alkyl or Cy² group, or together with the nitrogen atom to

25 unsaturated cyclicamino ring optionally containing one or more -O- or -S- atoms

or -NH- or -C(X^a)- groups), -C(X^a)NR^{1a}R^{2a}, -S(O)₂NR^{1a}R^{2a}, -N(R^{3a})C(X^a)R^{1a}R^{2a}
 (where R^{3a} is a hydrogen atom or an optionally substituted alkyl group),
 -N(R^{3a})C(X^a)NR^{1a}R^{2a}, -N(R^{3a})S(O)₂R¹, -N[S(O)₂R¹]₂, -N(R^{3a})S(O)₂NR^{1a}R^{2a},
 -N(R^{3a})C(O)OR¹, -N(R^{3a})C(NR¹)NR^{1a}R^{2a}, -C(R¹)NOR², -C(NR¹)NR^{1a}R^{2a},
 5 -C(X^a)NR^{1a}OR^{2a} or -C(O)N(R^{3a})NR^{1a}R^{2a} group];
 L is a -C(O)-, -C(S)- or -C(R^{1f})(R^{1g})- group [where R^{1f} and R^{1g}, which may be
 the same or different, is each a hydrogen atom or a straight or branched C₁-
 3alkyl group optionally substituted by one, two or three fluorine atoms, or R^{1f}
 and R^{1g} together with the carbon atom to which they are attached form a
 10 cyclopropyl group];
 n is zero or the integer 1;
 Alk¹ is an optionally substituted aliphatic or heteroaliphatic chain;
 L¹ is a covalent bond or a linker atom or group;
 Cy¹ is an optionally substituted cycloaliphatic, polycycloaliphatic,
 15 heterocycloaliphatic, polyheterocycloaliphatic, aromatic or heteroaromatic
 group, or is additionally a hydrogen atom when n is the integer 1 and/or L¹ is
 a linker atom or group;
 Ar is an optionally substituted aromatic or heteroaromatic group;
 provided that the compound of formula (1) is other than 3,7-dibenzyl-3,7-
 20 dihydro-2H-purinone;
 and the salts, solvates, hydrates and N-oxides thereof;

It will be appreciated that compounds of formula (1) may have one or more
 chiral centres, and exist as enantiomers or diastereomers. The invention is to
 25 be understood to extend to all such enantiomers, diastereomers and mixtures
 thereof, including racemates. Formula (1) and the formulae hereinafter are
 intended to represent all individual isomers and mixtures thereof, unless
 stated or shown otherwise. In addition, compounds of formula (1) may exist
 as tautomers, for example keto (CH₂C=O) - enol (CH=CHOH) tautomers.
 30 Formula (1) and the formulae hereinafter are intended to represent all
 individual tautomers and mixtures thereof, unless stated otherwise.

The following general terms as used herein in relation to compounds of the invention and intermediates thereto have the stated meaning below unless specifically defined otherwise.

5

Thus as used herein the term "alkyl" whether present as a group or part of a group includes straight or branched C₁₋₆alkyl groups, for example C₁₋₄alkyl groups such as methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, i-butyl or t-butyl groups. Similarly, the terms "alkenyl" or "alkynyl" are intended to mean
10 straight or branched C₂₋₆alkenyl or C₂₋₆alkynyl groups such as C₂₋₄alkenyl or C₂₋₄alkynyl groups.

Optional substituents which may be present on any of these alkyl, alkenyl or alkynyl groups include one, two, three or more substituents where each
15 substituent may be the same or different and is selected from a halogen atom or an -OH, -CO₂H, -CO₂R⁴ [where R⁴ is an optionally substituted straight or branched C₁₋₆alkyl group], -CONH₂, -CONHR⁴, -CON(R⁴)₂, -COR⁴, C₁₋₆alkoxy, haloC₁₋₆alkoxy, -S(O)R⁴, -S(O)₂R⁴, C₁₋₆alkylthio, -NH₂, -NHR⁴,
-N(R⁴)₂, -S(O)₂NH₂, -S(O)₂NHR⁴, -S(O)₂N(R⁴)₂, -NHC(O)R⁴, -N(R⁴)C(O)R⁴,
20 -NHS(O)₂R⁴, -N(R⁴)S(O)₂R⁴, -NHS(O)₂NH₂, -NHS(O)₂NHR⁴, -NHS(O)₂N(R⁴)₂,
-N(R⁴)S(O)₂NH₂, -N(R⁴)S(O)₂NHR⁴ or -N(R⁴)S(O)₂N(R⁴)₂ group. Where two R⁴ groups are present in a group, these may be the same or different or may be joined, together with the N atom to which they are attached, to form a heterocyclic ring. Such heterocyclic rings may be optionally interrupted by a
25 further heteroatom or heteroatom containing group selected from -O-, -S-, -NH-, -N(R⁴)-, -C(O)- or -C(S)- groups. Particular examples of such heterocyclic rings include piperidinyl, pyrazolidinyl, morpholinyl, thiomorpholinyl, pyrrolidinyl, imidazolidinyl or piperazinyl rings.

30 The term "halogen" as used herein is intended to include fluorine, chlorine, bromine or iodine atoms.

The term "haloalkyl" is intended to include those alkyl groups particularly mentioned above substituted by one, two or three of the halogen atoms just described. Particular examples of such groups include $-\text{CF}_3$, $-\text{CCl}_3$, $-\text{CHF}_2$, $-\text{CHCl}_2$, $-\text{CH}_2\text{F}$ and $-\text{CH}_2\text{Cl}$ groups. Each haloalkyl group may be optionally substituted by one or more hydroxyl groups and the term is to be understood to include such substituted groups, such as $-\text{C}(\text{OH})(\text{CF}_3)_2$ groups.

The term "alkoxy" as used herein is intended to include straight or branched C_{1-6} alkoxy e.g. C_{1-4} alkoxy such as methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, s-butoxy, i-butoxy and t-butoxy. "Haloalkoxy" as used herein includes any of these alkoxy groups substituted by one, two or three halogen atoms as described above. Particular examples include $-\text{OCF}_3$, $-\text{OCCl}_3$, $-\text{OCHF}_2$, $-\text{OCHCl}_2$, $-\text{OCH}_2\text{F}$ and $-\text{OCH}_2\text{Cl}$ groups.

As used herein the term "alkylthio" is intended to include straight or branched C_{1-6} alkylthio, e.g. C_{1-4} alkylthio such as methylthio or ethylthio.

When Alk^1 is present in compounds of formula (1) as an optionally substituted aliphatic chain it may be an optionally substituted C_{1-10} aliphatic chain. Particular examples include optionally substituted straight or branched chain C_{1-6} alkylene, C_{2-6} alkenylene, or C_{2-6} alkynylene chains.

Particular examples of aliphatic chains represented by Alk^1 include optionally substituted $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}(\text{CH}_3)\text{CH}_2-$, $-(\text{CH}_2)_2\text{CH}_2-$, $-(\text{CH}_2)_3\text{CH}_2-$, $-\text{CH}(\text{CH}_3)(\text{CH}_2)_2\text{CH}_2-$, $-\text{CH}_2\text{CH}(\text{CH}_3)\text{CH}_2-$, $-\text{C}(\text{CH}_3)_2\text{CH}_2-$, $-\text{CH}_2\text{C}(\text{CH}_3)_2\text{CH}_2-$, $-(\text{CH}_2)_2\text{CH}(\text{CH}_3)\text{CH}_2-$, $-\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_2-$, $-\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}(\text{CH}_3)\text{CH}_2-$, $-\text{CH}_2\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_2-$, $-(\text{CH}_2)_2\text{C}(\text{CH}_3)_2\text{CH}_2-$, $-(\text{CH}_2)_4\text{CH}_2-$, $-(\text{CH}_2)_5\text{CH}_2-$, $-\text{CHCH}-$, $-\text{CHCHCH}_2-$, $-\text{CH}_2\text{CHCH}-$, $-\text{CHCHCH}_2\text{CH}_2-$, $-\text{CH}_2\text{CHCHCH}_2-$, $-(\text{CH}_2)_2\text{CHCH}-$, $-\text{CC}-$, $-\text{CCCH}_2-$, $-\text{CH}_2\text{CC}-$, $-\text{CCCH}_2\text{CH}_2-$, $-\text{CH}_2\text{CCCH}_2-$ or $-(\text{CH}_2)_2\text{CCH}-$ chains.

Heteroaliphatic chains represented by Alk^1 in the compounds of formula (1) include the aliphatic chains just described but with each additionally containing one, two, three or four heteroatoms or heteroatom-containing groups. Particular heteroatoms or groups include atoms or groups L^2 where L^2 is a linker atom or group. Each L^2 atom or group may interrupt the aliphatic group, or may be positioned at its terminal carbon atom to connect the group to an adjoining atom or group. Particular examples include optionally substituted $-\text{L}^2\text{CH}_2-$, $-\text{CH}_2\text{L}^2-$, $-\text{L}^2\text{CH}(\text{CH}_3)-$, $-\text{CH}(\text{CH}_3)\text{L}^2-$, $-\text{CH}_2\text{L}^2\text{CH}_2-$, $-\text{L}^2\text{CH}_2\text{CH}_2-$, $-\text{L}^2\text{CH}_2\text{CH}(\text{CH}_3)-$, $-\text{CH}(\text{CH}_3)\text{CH}_2\text{L}^2-$, $-\text{CH}_2\text{CH}_2\text{L}^2-$, $-\text{CH}_2\text{L}^2\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{L}^2\text{CH}_2\text{CH}_2\text{L}^2-$, $-(\text{CH}_2)_2\text{L}^2\text{CH}_2-$, $-(\text{CH}_2)_3\text{L}^2\text{CH}_2-$, $-\text{L}^2(\text{CH}_2)_2\text{CH}_2-$, $-\text{L}^2\text{CH}_2\text{CHCH}-$, $-\text{CHCHCH}_2\text{L}^2-$ and $-(\text{CH}_2)_2\text{L}^2\text{CH}_2\text{CH}_2-$ chains.

When L^2 is present in heteroaliphatic chains as a linker atom or group it may be any divalent linking atom or group. Particular examples include $-\text{O}-$ or $-\text{S}-$ atoms or $-\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{O}-$, $-\text{OC}(\text{O})-$, $-\text{C}(\text{S})-$, $-\text{S}(\text{O})-$, $-\text{S}(\text{O})_2-$, $-\text{N}(\text{R}^3)-$ [where R^3 is a hydrogen atom or a straight or branched alkyl group], $-\text{N}(\text{R}^3)\text{O}-$, $-\text{N}(\text{R}^3)\text{N}-$, $-\text{CON}(\text{R}^3)-$, $-\text{OC}(\text{O})\text{N}(\text{R}^3)-$, $-\text{CSN}(\text{R}^3)-$, $-\text{N}(\text{R}^3)\text{CO}-$, $-\text{N}(\text{R}^3)\text{C}(\text{O})\text{O}-$, $-\text{N}(\text{R}^3)\text{CS}-$, $-\text{S}(\text{O})_2\text{N}(\text{R}^3)-$, $-\text{N}(\text{R}^3)\text{S}(\text{O})_2-$, $-\text{N}(\text{R}^3)\text{CON}(\text{R}^3)-$, $-\text{N}(\text{R}^3)\text{CSN}(\text{R}^3)-$ or $-\text{N}(\text{R}^3)\text{SO}_2\text{N}(\text{R}^3)-$ groups. Where L^2 contains two R^3 groups these may be the same or different.

The optional substituents which may be present on aliphatic or heteroaliphatic chains represented by Alk^1 include one, two or three of those optional substituents described above in relation to the term "alkyl".

When X or Y in compounds of the invention contain an Alk^2 chain, the chain may be an optionally substituted, straight or branched C_{1-6} alkylene, C_{2-6} alkenylene or C_{2-6} alkynylene chain. Particular chains include those just described above for the chain Alk^1 . Where desired each chain may be substituted by one, two or three substituents as described for Alk^1 .

When a carbocyclic non-aromatic ring Cy^2 is present in compounds of formula (1) it may be an optionally substituted C_{3-7} cycloalkyl, C_{3-7} cycloalkenyl, C_{3-7} heterocycloalkyl or C_{3-7} heterocycloalkenyl ring as generally and particularly described hereinafter in relation to the group Cy^1 . Optional substituents, which may be present on any available carbon or nitrogen atom in the ring, include those described above in relation to the term "alkyl".

Similarly, when $-NR^{1a}R^{2a}$ is present in compounds of the invention as a cyclicamino ring it may be an optionally substituted C_{3-7} cycloalkylamino, C_{3-7} cycloalkenylamino, C_{3-7} heterocycloalkylamino or C_{3-7} heterocycloalkenylamino ring as generally and particularly described below in relation to the group Cy^1 . Each ring may be optionally substituted on any available ring carbon or nitrogen atom by a substituent selected from those described above in relation to the term "alkyl".

When L^1 is present in compounds of formula (1) as a linker atom or group it may be any such atom or group as hereinbefore described in relation to L^2 linker atoms and groups.

Optionally substituted cycloaliphatic groups represented by the group Cy^1 in compounds of the invention include optionally substituted C_{3-10} cycloaliphatic groups. Particular examples include optionally substituted C_{3-10} cycloalkyl, e.g. C_{3-7} cycloalkyl or C_{3-10} cycloalkenyl, e.g. C_{3-7} cycloalkenyl groups.

Optionally substituted heterocycloaliphatic groups represented by the group Cy^1 include optionally substituted C_{3-10} heterocycloaliphatic groups. Particular examples include optionally substituted C_{3-10} heterocycloalkyl, e.g. C_{3-7} heterocycloalkyl or C_{3-10} heterocycloalkenyl, e.g. C_{3-7} heterocycloalkenyl groups, each of said groups containing one, two, three or four heteroatoms or

heteroatom containing groups L^4 in place of or in addition to the ring carbon atoms, where L^4 is an atom or group as just defined above for L^2 .

Optionally substituted polycycloaliphatic groups represented by the group Cy^1 include optionally substituted $C_{7-10}bi$ - or tricycloalkyl or $C_{7-10}bi$ - or tricycloalkenyl groups. Optionally substituted heteropolycycloaliphatic groups represented by the group Cy^1 include optionally substituted $C_{7-10}bi$ - or tricycloalkyl or $C_{7-10}bi$ - or tri-cycloalkenyl groups containing one, two, three, four or more L^4 atoms or groups in place of or in addition to the ring carbon atoms.

Particular examples of cycloaliphatic, polycycloaliphatic, heterocycloaliphatic and heteropolycycloaliphatic groups represented by the group Cy^1 include optionally substituted cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, 2-cyclobuten-1-yl, 2-cyclopenten-1-yl, 3-cyclopenten-1-yl, adamantyl, norbornyl, norbornenyl, dihydrofuranyl, tetrahydrofuranyl, tetrahydropyranyl, dihydrothiophenyl, tetrahydrothiophenyl, pyrroline, e.g. 2- or 3-pyrrolinyl, pyrrolidinyl, pyrrolidinone, oxazolidinyl, oxazolidinone, dioxolanyl, e.g. 1,3-dioxolanyl, imidazolanyl, e.g. 2-imidazolanyl, imidazolidinyl, pyrazolanyl, e.g. 2-pyrazolanyl, pyrazolidinyl, 5,6-dihydro-2(1H)-pyrazinone, tetrahydropyrimidinyl, thiazolanyl, thiazolidinyl, pyranal, e.g. 2- or 4-pyranal, piperidinyl, homopiperidinyl, heptamethyleneiminyl, piperidinone, 1,4-dioxanyl, morpholanyl, morpholinone, 1,4-dithianyl, thiomorpholanyl, piperazinyl, homopiperazinyl, 1,3,5-trithianyl, oxazinyl, e.g. 2H-1,3-, 6H-1,3-, 6H-1,2-, 2H-1,2- or 4H-1,4-oxazinyl, 1,2,5-oxathiazinyl, isoxazinyl, e.g. o- or p-isoxazinyl, oxathiazinyl, e.g. 1,2,5 or 1,2,6-oxathiazinyl, 1,3,5-oxadiazinyl, dihydroisothiazolyl, dihydroisothiazole 1,1-dioxide, e.g. 2,3-dihydroisothiazole 1,1-dioxide, dihydropyrazinyl and tetrahydropyrazinyl groups.

The optional substituents which may be present on the cycloaliphatic, polycycloaliphatic, heterocycloaliphatic or heteropolycycloaliphatic groups represented by the group Cy¹ include one, two, three or more substituents selected from halogen atoms, or C₁₋₆alkyl, e.g. methyl or ethyl, haloC₁₋₆alkyl, e.g. halomethyl or haloethyl such as difluoromethyl or trifluoromethyl, optionally substituted by hydroxyl, e.g. -C(OH)(CF₃)₂, C₁₋₆alkoxy, e.g. methoxy or ethoxy, haloC₁₋₆alkoxy, eg. halomethoxy or haloethoxy such as difluoromethoxy or trifluoromethoxy, thiol, C₁₋₆alkylthiol, e.g. methylthiol or ethylthiol, carbonyl (=O), thiocarbonyl (=S), imino (=NR^{4a}) [where R^{4a} is an -OH group or a C₁₋₆alkyl group], or -(Alk³)_vR⁵ groups in which Alk³ is a straight or branched C₁₋₃alkylene chain, v is zero or the integer 1 and R⁵ is a C₃₋₈cycloalkyl, -OH, -SH, -N(R⁶)(R⁷) [in which R⁶ and R⁷ is each independently selected from a hydrogen atom or an optionally substituted alkyl or C₃₋₈cycloalkyl group], -OR⁶, -SR⁶, -CN, -NO₂, -CO₂R⁶, -SOR⁶, -SO₂R⁶, -SO₃R⁶, -OCO₂R⁶, -C(O)R⁶, -OC(O)R⁶, -C(S)R⁶, -C(O)N(R⁶)(R⁷), -OC(O)N(R⁶)(R⁷), -N(R⁶)C(O)R⁷, -C(S)N(R⁶)(R⁷), -N(R⁶)C(S)R⁷, -SO₂N(R⁶)(R⁷), -N(R⁶)SO₂R⁷, -N(R⁶)C(O)N(R⁷)(R⁸) [where R⁸ is as defined for R⁶], -N(R⁶)C(S)N(R⁷)(R⁸), -N(R⁶)SO₂N(R⁷)(R⁸) or an optionally substituted aromatic or heteroaromatic group.

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Particular examples of Alk³ chains include -CH₂-, -CH₂CH₂-, -CH₂CH₂CH₂- and -CH(CH₃)CH₂- chains.

When R⁵, R⁶, R⁷ and/or R⁸ is present as a C₃₋₈cycloalkyl group it may be for example a cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl group. Optional substituents which may be present on such groups include for example one, two or three substituents which may be the same or different selected from halogen atoms, for example fluorine, chlorine, bromine or iodine atoms, or hydroxy or C₁₋₆alkoxy, e.g. methoxy, ethoxy or *i*-propoxy groups.

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When the groups R^6 and R^7 or R^7 and R^8 are both alkyl groups these groups may be joined, together with the N atom to which they are attached, to form a heterocyclic ring. Such heterocyclic rings may be optionally interrupted by a further heteroatom or heteroatom containing group selected from $-O-$, $-S-$, $-N(R^7)-$, $-C(O)-$ or $-C(S)-$ groups. Particular examples of such heterocyclic rings include piperidinyl, pyrazolidinyl, morpholinyl, thiomorpholinyl, pyrrolidinyl, imidazolidinyl and piperazinyl rings.

When R^5 is an optionally substituted aromatic or heteroaromatic group it may be any such group as described hereinafter in relation to Cy^1 .

Additionally, when the group Cy^1 is a heterocycloaliphatic or heteropolycycloaliphatic group containing one or more nitrogen atoms each nitrogen atom may be optionally substituted by a group $-(L^5)_p(Alk^4)_qR^9$ in which L^5 is a $-C(O)-$, $-C(O)O-$, $-C(S)-$, $-S(O)_2-$, $-CON(R^6)-$ or $-SO_2N(R^6)-$ group; p is zero or the integer 1; Alk^4 is an optionally substituted aliphatic or heteroaliphatic chain; q is zero or the integer 1; and R^9 is a hydrogen atom or an optionally substituted cycloaliphatic, heterocycloaliphatic, polycycloaliphatic, heteropolycycloaliphatic, aromatic or heteroaromatic group as herein described in relation to Cy^1 .

When Alk^4 is present as an aliphatic or heteroaliphatic chain it may be for example any aliphatic or heteroaliphatic chain as hereinbefore described for Alk^1 .

Optionally substituted aromatic groups represented by the groups Cy^1 include for example monocyclic or bicyclic fused ring C_{6-12} aromatic groups, such as phenyl, 1- or 2-naphthyl, 1- or 2-tetrahydronaphthyl, indanyl or indenyl groups.

Heteroaromatic groups represented by the groups Cy^1 include for example C_{1-9} heteroaromatic groups containing for example one, two, three or four

- heteroatoms selected from oxygen, sulphur or nitrogen atoms. In general, the heteroaromatic groups may be for example monocyclic or bicyclic fused ring heteroaromatic groups. Monocyclic heteroaromatic groups include for example five- or six-membered heteroaromatic groups containing one, two, three or four heteroatoms selected from oxygen, sulphur or nitrogen atoms. Bicyclic heteroaromatic groups include for example eight- to thirteen-membered fused ring heteroaromatic groups containing one, two or more heteroatoms selected from oxygen, sulphur or nitrogen atoms.
- Particular examples of heteroaromatic groups of these types include pyrrolyl, furyl, thienyl, imidazolyl, N-C₁₋₆alkylimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,3-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,3,4-thiadiazolyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, 1,3,5-triazinyl, 1,2,4-triazinyl, 1,2,3-triazinyl, benzofuryl, [2,3-dihydro]benzofuryl, benzothienyl, [2,3-dihydro]benzothienyl, benzotriazolyl, indolyl, indolinyl, indazolyl, benzimidazolyl, imidazo[1,2-a]pyridyl, benzothiazolyl, benzoxazolyl, benzisoxazolyl, benzopyranyl, [3,4-dihydro]benzopyranyl, quinazolinyl, quinoxalinyl, naphthyridinyl, imidazo[1,5-a]pyridinyl, imidazo[1,5-a]pyrazinyl, imidazo[1,5-c]pyrimidinyl, pyrido[3,4-b]pyridyl, pyrido[3,2-b]pyridyl, pyrido[4,3-b]pyridyl, quinolinyl, isoquinolinyl, phthalazinyl, tetrazolyl, 5,6,7,8-tetrahydroquinolinyl, 5,6,7,8-tetrahydroisoquinolinyl, imidyl, e.g. succinimidyl, phthalimidyl or naphthalimidyl such as 1,8-naphthalimidyl, pyrazolo[4,3-d]pyrimidinyl, furo[3,2-d]pyrimidinyl, thieno[3,2-d]pyrimidinyl, pyrrolo[3,2-d]pyrimidinyl, pyrazolo[3,2-b]pyridinyl, furo[3,2-b]pyridinyl, thieno[3,2-b]pyridinyl, pyrrolo[3,2-b]pyridinyl, thiazolo[3,2-a]pyridinyl, pyrido[1,2-a]pyrimidinyl, tetrahydroimidazo[1,2-a]pyrimidinyl and dihydroimidazo[1,2-a]pyrimidinyl groups.
- Optional substituents which may be present on aromatic or heteroaromatic groups represented by the group Cy¹ include one, two, three or more

substituents, each selected from an atom or group R^{10} in which R^{10} is R^{10a} or $-L^6Alk^5(R^{10a})_r$, where R^{10a} is a halogen atom, or an amino ($-NH_2$), substituted amino, nitro, cyano, hydroxyl ($-OH$), substituted hydroxyl, formyl, carboxyl ($-CO_2H$), esterified carboxyl, thiol ($-SH$), substituted thiol, $-COR^{11}$ [where R^{11} is an $-L^6Alk^3(R^{10a})_r$, aryl or heteroaryl group], $-CSR^{11}$, $-SO_3H$, $-SOR^{11}$, $-SO_2R^{11}$, $-SO_3R^{11}$, $-SO_2NH_2$, $-SO_2NHR^{11}$, $-SO_2N(R^{11})_2$, $-CONH_2$, $-CSNH_2$, $-CONHR^{11}$, $-CSNHR^{11}$, $-CON(R^{11})_2$, $-CSN(R^{11})_2$, $-N(R^{12})SO_2R^{11}$ [where R^{12} is a hydrogen atom or a straight or branched alkyl group], $-N(SO_2R^{11})_2$, $-N(R^{12})SO_2NH_2$, $-N(R^{12})SO_2NHR^{11}$, $-N(R^{12})SO_2N(R^{11})_2$, $-N(R^{12})COR^{11}$, $-N(R^{12})CONH_2$, $-N(R^{12})CONHR^{11}$, $-N(R^{12})CON(R^{11})_2$, $-N(R^{12})CSNH_2$, $-N(R^{12})CSNHR^{11}$, $-N(R^{12})CSN(R^{11})_2$, $-N(R^{12})CSR^{11}$, $-N(R^{12})C(O)OR^{11}$, $-SO_2NHet^1$ [where $-NHet^1$ is an optionally substituted C_{5-7} cyclicamino group optionally containing one or more other $-O-$ or $-S-$ atoms or $-N(R^{12})-$, $-C(O)-$ or $-C(S)-$ groups], $-CONHet^1$, $-CSNHet^1$, $-N(R^{12})SO_2NHet^1$, $-N(R^{12})CONHet^1$, $-N(R^{12})CSNHet^1$, $-SO_2N(R^{12})Het$ [where $-Het$ is an optionally substituted monocyclic C_{5-7} carbocyclic group optionally containing one or more other $-O-$ or $-S-$ atoms or $-N(R^{12})-$, $-C(O)-$, $-S(O)-$ or $-S(O)_2-$ groups], $-Het$, $-CON(R^{12})Het$, $-CSN(R^{12})Het$, $-N(R^{12})CON(R^{12})Het$, $-N(R^{12})CSN(R^{12})Het$, $-N(R^{12})SO_2N(R^{12})Het$, aryl or heteroaryl groups; L^6 is a covalent bond or a linker atom or group as hereinbefore defined for L^2 ; Alk^5 is an optionally substituted straight or branched C_{1-6} alkylene, C_{2-6} alkenylene or C_{2-6} alkynylene chain, optionally interrupted by one, two or three $-O-$ or $-S-$ atoms or $-S(O)_n-$ [where n is an integer 1 or 2] or $-N(R^{12})-$ e.g. $-N(CH_3)-$ groups; and r is zero or the integer 1, 2, or 3. It will be appreciated that when two R^{11} or R^{12} groups are present in one of the above substituents the R^{11} and R^{12} groups may be the same or different.

When in the group $-L^6Alk^5(R^{10a})_r$, r is an integer 1, 2 or 3, it is to be understood that the substituent or substituents R^{10a} may be present on any suitable carbon atom in $-Alk^5$. Where more than one R^{10a} substituent is present these may be the same or different and may be present on the same or different atom in $-$

Alk⁵. Clearly, when r is zero and no substituent R^{10a} is present the alkylene, alkenylene or alkynylene chain represented by Alk⁵ becomes an alkyl, alkenyl or alkynyl group.

- 5 When R^{10a} is a substituted amino group it may be for example a group -NHR¹¹ [where R¹¹ is as defined above] or a group -N(R¹¹)₂ wherein each R¹¹ group is the same or different.

- When R^{10a} is a halogen atom it may be for example a fluorine, chlorine,
10 bromine, or iodine atom.

When R^{10a} is a substituted hydroxyl or substituted thiol group it may be for example a group -OR¹¹ or a -SR¹² group respectively.

- 15 Esterified carboxyl groups represented by the group R^{10a} include groups of formula -CO₂Alk⁶ wherein Alk⁶ is a straight or branched, optionally substituted C₁₋₈alkyl group such as a methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl or t-butyl group; a C₆₋₁₂arylC₁₋₈alkyl group such as an optionally substituted benzyl, phenylethyl, phenylpropyl, 1-naphthylmethyl or 2-naphthylmethyl group;
20 a C₆₋₁₂aryl group such as an optionally substituted phenyl, 1-naphthyl or 2-naphthyl group; a C₆₋₁₂aryloxyC₁₋₈alkyl group such as an optionally substituted phenyloxymethyl, phenyloxyethyl, 1-naphthyloxymethyl, or 2-naphthyloxymethyl group; an optionally substituted C₁₋₈alkanoyloxyC₁₋₈alkyl group, such as a pivaloyloxymethyl, propionyloxyethyl or propionyloxypropyl group; or a C₆₋
25 ₁₂aroyloxyC₁₋₈alkyl group such as an optionally substituted benzoyloxyethyl or benzoyloxypropyl group. Optional substituents present on the Alk⁶ group include R^{10a} atoms and groups as described above.

- When Alk⁵ is present in or as a substituent it may be for example a -CH₂-, -
30 CH(CH₃)-, -C(CH₃)₂-, -CH₂CH₂-, -CH₂CH₂CH₂-, -CH(CH₃)CH₂-, -CH₂CH₂CH₂CH₂-, -CH₂CH(CH₃)CH₂-, -CH(CH₃)CH₂CH₂-, -C(CH₃)₂CH₂-, -

CH=CH-, -CH=CCH₂-, -CH₂C=CH-, -CH=CHCH₂CH₂-, -CH₂CH=CHCH₂-, -CH₂CH₂CH=CH₂-, -CC-, -CCCH₂-, -CH₂CC-, -CCCH₂CH₂-, -CH₂CCCH₂- or -CH₂CH₂CC- chain, optionally interrupted by one, two, or three -O- or -S-, atoms or -S(O)-, -S(O)₂- or -N(R¹²)-, e.g. -N(CH₃)- groups. The aliphatic chains
5 represented by Alk⁵ may be optionally substituted by one, two or three halogen atoms in addition to any R^{10a} groups that may be present.

Aryl or heteroaryl groups represented by the groups R^{10a} or R¹¹ include mono- or bicyclic optionally substituted C₆₋₁₂ aromatic or C₁₋₉ heteroaromatic groups as
10 described above for the group Cy¹. The aromatic and heteroaromatic groups may be attached to the group Cy¹ in compounds of formula (1) by any carbon or hetero e.g. nitrogen atom as appropriate.

It will be appreciated that when -NHet¹ or -Het forms part of a substituent R¹⁰
15 the heteroatoms or heteroatom containing groups that may be present within the ring -NHet¹ or -Het take the place of carbon atoms within the parent carbocyclic ring.

Thus when -NHet¹ or -Het forms part of a substituent R¹⁰ each may be for
20 example an optionally substituted pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, piperidinyl or thiazolidinyl group. Additionally Het may represent for example, an optionally substituted cyclopentyl or cyclohexyl group. Optional substituents which may be present on -NHet¹ include those substituents described above when Cy¹ is a
25 heterocycloaliphatic group.

Particularly useful atoms or groups represented by R¹⁰ include fluorine, chlorine, bromine or iodine atoms, or C₁₋₆alkyl, e.g. methyl, ethyl, n-propyl, i-propyl, n-butyl or t-butyl, optionally substituted phenyl, pyridyl, pyrimidinyl, pyrrolyl, furyl,
30 thiazolyl, or thienyl, C₁₋₆hydroxyalkyl, e.g. hydroxymethyl or hydroxyethyl, carboxyC₁₋₆alkyl, e.g. carboxyethyl, C₁₋₆alkylthio e.g. methylthio or ethylthio,

carboxyC₁₋₆alkylthio, e.g. carboxymethylthio, 2-carboxyethylthio or 3-carboxypropylthio, C₁₋₆alkoxy, e.g. methoxy or ethoxy, hydroxyC₁₋₆alkoxy, e.g. 2-hydroxyethoxy, optionally substituted phenoxy, pyridyloxy, thiazolyoxy, phenylthio or pyridylthio, C₃₋₇cycloalkyl, e.g. cyclobutyl, cyclopentyl, C₅₋₇cycloalkoxy, e.g. cyclopentylloxy, haloC₁₋₆alkyl, e.g. trifluoromethyl, haloC₁₋₆alkoxy, e.g. trifluoromethoxy, C₁₋₆alkylamino, e.g. methylamino, ethylamino, -CH(CH₃)NH₂ or -C(CH₃)₂NH₂, haloC₁₋₆alkylamino, e.g. fluoroC₁₋₆alkylamino, e.g. -CH(CF₃)NH₂ or -C(CF₃)₂NH₂, amino (-NH₂), aminoC₁₋₆alkyl, e.g. aminomethyl or aminoethyl, C₁₋₆dialkylamino, e.g. dimethylamino or diethylamino, C₁₋₆alkylaminoC₁₋₆alkyl, e.g. ethylaminoethyl, C₁₋₆dialkylaminoC₁₋₆alkyl, e.g. diethylaminoethyl, aminoC₁₋₆alkoxy, e.g. aminoethoxy, C₁₋₆alkylaminoC₁₋₆alkoxy, e.g. methylaminoethoxy, C₁₋₆dialkylaminoC₁₋₆alkoxy, e.g. dimethylaminoethoxy, diethylaminoethoxy, diisopropylaminoethoxy, or dimethylaminopropoxy, imido, such as phthalimido or naphthalimido, e.g. 1,8-naphthalimido, nitro, cyano, hydroxyl (-OH), formyl [HC(O)-], carboxyl (-CO₂H), -CO₂Alk⁶ [where Alk⁶ is as defined above], C₁₋₆alkanoyl e.g. acetyl, optionally substituted benzoyl, thiol (-SH), thioC₁₋₆alkyl, e.g. thiomethyl or thioethyl, sulphonyl (-SO₃H), C₁₋₆alkylsulphonyl, e.g. methylsulphonyl, aminosulphonyl (-SO₂NH₂), C₁₋₆alkylaminosulphonyl, e.g. methylaminosulphonyl or ethylaminosulphonyl, C₁₋₆dialkylaminosulphonyl, e.g. dimethylaminosulphonyl or diethylaminosulphonyl, phenylaminosulphonyl, carboxamido (-CONH₂), C₁₋₆alkylaminocarbonyl, e.g. methylaminocarbonyl or ethylaminocarbonyl, C₁₋₆dialkylaminocarbonyl, e.g. dimethylaminocarbonyl or diethylaminocarbonyl, aminoC₁₋₆alkylaminocarbonyl, e.g. aminoethylamino-carbonyl, C₁₋₆dialkylaminoC₁₋₆alkylaminocarbonyl, e.g. diethylaminoethyl-aminocarbonyl, aminocarbonylamino, C₁₋₆alkylaminocarbonylamino, e.g. methylaminocarbonylamino or ethylaminocarbonylamino, C₁₋₆dialkylamino-carbonylamino, e.g. dimethylaminocarbonylamino or diethylamino-carbonylamino, C₁₋₆alkylaminocarbonylC₁₋₆alkylamino, e.g. methylamino-carbonylmethylamino, aminothiocarbonylamino, C₁₋₆alkylaminothiocarbonyl-amino, e.g. methylaminothiocarbonylamino or ethylaminothiocarbonylamino, C₁₋

5 dialkylaminothiocarbonylamino, e.g. dimethylaminothiocarbonylamino or diethylaminothiocarbonylamino, C₁₋₆alkylaminothiocarbonylC₁₋₆alkylamino, e.g. ethylaminothiocarbonylmethylamino, -CONHC(=NH)NH₂, C₁₋₆alkylsulphonylamino, e.g. methylsulphonylamino or ethylsulphonylamino, C₁₋₆dialkylsulphonylamino, e.g. dimethylsulphonylamino or diethylsulphonylamino, optionally substituted phenylsulphonylamino, aminosulphonylamino (-NHSO₂NH₂), C₁₋₆alkylaminosulphonylamino, e.g. methylaminosulphonylamino or ethylaminosulphonylamino, C₁₋₆dialkylaminosulphonylamino, e.g. dimethylaminosulphonylamino or diethylaminosulphonylamino, optionally substituted morpholinesulphonylamino or morpholinesulphonylC₁₋₆alkylamino, optionally substituted phenylaminosulphonylamino, C₁₋₆alkanoylamino, e.g. acetylamino, aminoC₁₋₆alkanoylamino e.g. aminoacetylamino, C₁₋₆dialkylaminoC₁₋₆alkanoylamino, e.g. dimethylaminoacetylamino, C₁₋₆alkanoylaminoC₁₋₆alkyl, e.g. acetylaminomethyl, C₁₋₆alkanoylaminoC₁₋₆alkylamino, e.g. acetamidoethylamino, C₁₋₆alkoxycarbonylamino, e.g. methoxycarbonylamino, ethoxycarbonylamino or t-butoxycarbonylamino or optionally substituted benzyloxy, pyridylmethoxy, thiazolylmethoxy, benzyloxycarbonylamino, benzyloxycarbonylaminoC₁₋₆alkyl e.g. benzyloxycarbonylaminoethyl, benzothio, pyridylmethylthio or thiazolylmethylthio groups.

20

A further particularly useful group of substituents represented by R¹⁰ when present on aromatic or heteroaromatic groups includes substituents of formula -L⁶Alk⁵R^{10a} where L⁶ is preferably a covalent bond or an -O- or -S- atom or -N(R³)-, -C(O)-, -C(O)O-, -O-C(O)-, -N(R³)CO-, -CON(R³)- or -N(R³)S(O)₂- group, Alk⁵ is an optionally substituted C₁₋₆alkyl group optionally interrupted by one or two -O- or -S- atoms or -N(R¹²)-, -C(O)-, -C(S)-, -CON(R¹²)- or -N(R¹²)CO- groups and R^{10a} is an optionally substituted Het group as herein defined or an optionally substituted heteroaromatic group as hereinbefore described in relation to Cy¹.

30

Where desired, two R^{10} substituents may be linked together to form a cyclic group such as a cyclic ether, e.g. a C_{1-6} alkylenedioxy group such as methylenedioxy or ethylenedioxy.

- 5 It will be appreciated that where two or more R^{10} substituents are present, these need not necessarily be the same atoms and/or groups. In general, the substituent(s) may be present at any available ring position on the aromatic or heteroaromatic group represented by the group Cy^1 .
- 10 As used above the terms "alkylamino or dialkylamino" are intended to include the groups $-NHR^{13}$ and $-N(R^{13})(R^{14})$ respectively where R^{13} and R^{14} is each independently an optionally substituted straight or branched alkyl group or both together with the N atom to which they are attached form an optionally substituted heterocycloalkyl group which may contain a further heteroatom or
- 15 heteroatom containing group such as an -O- or -S- atom or $-N(R^{2a})$ - group. Particular examples of such optionally substituted heterocycloalkyl groups include optionally substituted pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl and N' - C_{1-6} alkyl-piperazinyl groups. The optional substituents which may be present on such heterocycloalkyl groups include those optional
- 20 substituents as described hereinafter in relation to aliphatic chains such as Alk^1 .

The substituted aromatic or heteroaromatic group represented by Ar in compounds of the invention may be any aromatic or heteroaromatic group as

25 hereinbefore generally or particularly described for Cy^1 . Optional substituents which may be present include those R^{10} atoms and groups as generally or particularly described in relation to Cy^1 aromatic and heteroaromatic groups.

In general in compounds of formula (1) X and Y is each preferably a $-C(R^e)=$ or $-C(Alk^2R^e)=$ group. R^e in these compounds is especially a hydrogen atom

30 or a $-CONR^{1a}R^{2a}$ or $-S(O)_2NR^{1a}R^{2a}$ group. Alk^2 when present is in particular a

-CH₂- or -(CH₂)₂- chain.

In one preference X is a -CH= group and Y is a -C(R^e)= or -C(Alk²R^e)= group, especially where R^e is a hydrogen atom or a -CONR^{1a}R^{2a} or

5 -S(O)₂NR^{1a}R^{2a} group and Alk² is a -CH₂- or -(CH₂)₂- chain.

In one group of compounds of formula (1) the bond represented by the dashed line is present and A is a -C(R^b)= group. In these compounds R^b is preferably a hydrogen atom or a C₁₋₄alkyl group, especially a methyl, ethyl, n-propyl or i-propyl group. More particularly R^b is a methyl group or more especially a hydrogen atom.

10

One particularly useful class of compounds according to the invention has the formula (1) wherein A, X and Y is each a -CH= group and R^a, Alk¹, n, L¹, Cy¹, L and Ar are as generally or particularly defined herein and the salts, solvates, hydrates and N-oxides thereof.

15

In general in compounds of formula (1) R^a is preferably a hydrogen atom or a C₁₋₄alkyl group, especially a methyl, ethyl, n-propyl or i-propyl group. In particular R^a is a methyl group or more especially a hydrogen atom.

20

When in compounds of formula (1) n is the integer 1, Alk¹ is preferably an optionally substituted C₁₋₆alkylene chain, especially an optionally substituted -CH₂-, -CH₂CH₂-, -CH₂CH₂CH₂-, -CH(CH₃)CH₂- or -CH₂CH(CH₃)- chain, most especially a -CH₂- or -CH₂CH₂- chain.

25

In one class of compounds of formula (1) n is zero.

The group L¹ in compounds of formula (1) is preferably a covalent bond or an -O- or -S- atom or an -N(R³)-, especially -NH- or -N(CH₃)-, -C(O)-, -C(S)-, -

30

S(O)- or $\text{--S(O)}_2\text{--}$ group. More particularly L^1 is a covalent bond or an --O-- or --S-- atom or --NH-- group. L^1 is more especially preferably is a covalent bond.

5 Cy^1 in compounds of formula (1) is preferably an optionally substituted cycloaliphatic, aromatic or heteroaromatic group as hereinbefore generally and particularly defined.

10 Particularly preferred Cy^1 optionally substituted cycloaliphatic groups include optionally substituted C_{3-7} cycloalkyl groups, especially cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl groups.

15 Particularly preferred optional substituents which may be present on Cy^1 optionally substituted cycloaliphatic groups include halogen atoms, especially fluorine, chlorine or bromine atoms, or C_{1-6} alkyl groups, especially C_{1-3} alkyl groups, most especially a methyl group, or a halo C_{1-6} alkyl group, especially a fluoro C_{1-6} alkyl group, most especially a --CF_3 group, or a C_{1-6} alkoxy, especially methoxy, ethoxy, propoxy or i-propoxy group, or a halo C_{1-6} alkoxy, especially a fluoro C_{1-6} alkoxy, most especially a --OCF_3 group, or a cyano (--CN), esterified carboxyl, especially $\text{--CO}_2\text{CH}_3$ or $\text{--CO}_2\text{C}(\text{CH}_3)_3$, nitro (--NO_2),
20 amino (--NH_2), substituted amino, especially --NHCH_3 or $\text{--N}(\text{CH}_3)_2$, --C(O)R^6 , especially --C(O)CH_3 , or $\text{--N(R}^6\text{)C(O)R}^7$, especially --NHCOCH_3 group.

25 Particularly preferred Cy^1 aromatic groups include optionally substituted phenyl groups. Particularly preferred heteroaromatic groups include optionally substituted monocyclic heteroaromatic groups, especially optionally substituted five- or six-membered heteroaromatic groups containing one, two, three or four heteroatoms selected from oxygen, sulphur or nitrogen atoms. Particularly preferred optionally substituted monocyclic heteroaromatic groups include optionally substituted furyl, thienyl, pyrrolyl,
30 oxazolyl, thiazolyl, pyridyl, pyrimidinyl or triazinyl group.

Particularly preferred optional substituents which may be present on Cy¹ aromatic or heteroaromatic groups include atoms or groups -R^{10a} or -L⁶Alk⁵(R^{10a})_r, as hereinbefore defined. Particularly useful optional substituents include halogen atoms, especially fluorine, chlorine or bromine atoms, or C₁₋₆alkyl groups, especially C₁₋₃alkyl groups, most especially a methyl group, or a haloC₁₋₆alkyl group, especially a fluoroC₁₋₆alkyl group, most especially a -CF₃ group, or a C₁₋₆alkoxy, especially methoxy, ethoxy, propoxy or i-propoxy group, or a haloC₁₋₆alkoxy, especially a fluoroC₁₋₆alkoxy, most especially a -OCF₃ group, or a cyano (-CN), carboxyl (-CO₂H), esterified carboxyl (-CO₂Alk⁶), especially -CO₂CH₃, -CO₂CH₂CH₃, or -CO₂C(CH₃)₃, nitro (-NO₂), amino (-NH₂), substituted amino, especially -NHCH₃ or -N(CH₃)₂, -COR¹¹, especially -COCH₃, or -N(R¹²)COR¹¹, especially -NHCOCH₃ group.

Further preferred optional substituents which may be present on Cy¹ aromatic or heteroaromatic groups include groups of formula -L⁶Alk⁵(R^{10a})_r, in which r is the integer 1, L⁶ is a covalent bond or an -O- or -S- atom or a -N(R³)-, especially -NH- or -N(CH₃)-, -C(O)-, -C(S)-, -C(O)O-, -OC(O)-, -N(R³)CO-, especially -NHCO-, or -CON(R³)-, especially -CHNH-group, Alk⁵ is a C₁₋₆alkyl chain, especially a -CH₂-, -CH₂CH₂-, -CH₂CH₂CH₂- or -CH₂CH₂CH₂CH₂- chain and R^{10a} is a substituted hydroxyl group, especially a -OCH₃, -OCH₂CH₃ or -OCH(CH₃)₂ group or a substituted amino group, especially a -N(CH₃)₂ or -N(CH₂CH₃)₂ group or a -Het group, especially an optionally substituted monocyclic C₅₋₇carbocyclic group containing one, two or three -O-, -S-, -N(R¹²)-, especially -NH- or -N(CH₃)- or -C(O)- groups within the ring structure as previously described, most especially an optionally substituted pyrrolidinyl, imidazolidinyl, piperidinyl, e.g. N-methylpiperidinyl, morpholinyl, thiomorpholinyl or piperazinyl group or R^{10a} is an optionally substituted heteroaromatic group, especially a five- or six-membered monocyclic heteroaromatic group containing one, two, three or four heteroatoms selected from oxygen, sulphur or nitrogen atoms, such as optionally substituted pyrrolyl, furyl, thienyl, imidazolyl, triazolyl, pyridyl,

pyrimidinyl, triazinyl, pyridazinyl, or pyrazinyl group. Particularly preferred optional substituents on the -Het groups just described include hydroxyl (-OH) and carboxyl (-CO₂H) groups or those preferred optional substituents just described in relation to the group Cy¹.

- 5 In one particularly preferred group of compounds of formula (1) Cy¹ is an optionally substituted phenyl group, especially a phenyl group optionally substituted by one, two or three optional substituents where at least one, and preferably two optional substituents are located *ortho* to the bond joining Cy¹ to the remainder of the compound of formula (1). Particularly preferred *ortho*
- 10 substituents include halogen atoms, especially fluorine or chlorine atoms, or C₁₋₃alkyl groups, especially methyl groups, C₁₋₃alkoxy groups, especially methoxy, haloC₁₋₃alkyl groups, especially -CF₃, haloC₁₋₃alkoxy groups, especially -OCF₃, or cyano (-CN), groups. In this class of compounds a second or third optional substituent when present in a position other than the
- 15 *ortho* positions of the ring Cy¹ may be preferably an atom or group -R^{10a} or -L⁶Alk⁵(R^{10a})_r as herein generally and particularly described.

- Particularly preferred Ar aromatic groups in compounds of formula (1) include optionally substituted phenyl groups. Particularly preferred heteroaromatic
- 20 groups include optionally substituted monocyclic heteroaromatic groups, especially optionally substituted five- or six-membered heteroaromatic groups containing one, two, three or four heteroatoms selected from oxygen, sulphur or nitrogen atoms. Particularly preferred optionally substituted monocyclic heteroaromatic groups include optionally substituted furyl, thienyl, pyrrolyl,
- 25 oxazolyl, thiazolyl, pyridyl, pyrimidinyl or triazinyl group.

- Particularly preferred optional substituents which may be present on Ar aromatic or heteroaromatic groups include atoms or groups -R^{10a} or -L⁶Alk⁵(R^{10a})_r as hereinbefore defined. Particularly useful optional substituents
- 30 include halogen atoms, especially fluorine, chlorine or bromine atoms, or C₁-

alkyl groups, especially C₁₋₃alkyl groups, most especially a methyl group, or a haloC₁₋₆alkyl group, especially a fluoroC₁₋₆alkyl group, most especially a –CF₃ group, or a C₁₋₆alkoxy, especially methoxy, ethoxy, propoxy or i-propoxy group, or a haloC₁₋₆alkoxy, especially a fluoroC₁₋₆alkoxy, most especially a –OCF₃ group, or a cyano (–CN), esterified carboxyl, especially –CO₂CH₃ or –CO₂C(CH₃)₃, nitro (–NO₂), amino (–NH₂), substituted amino, especially –NHCH₃ or –N(CH₃)₂, –COR¹¹, especially –COCH₃, or –N(R¹²)COR¹¹, especially –NHCOCH₃ group.

10 Particularly useful Ar groups in compounds of formula (1) include phenyl and mono- or disubstituted phenyl groups in which each substituent is in particular a –R^{10a} or –L⁶Alk⁵(R^{10a})_r atom or group as just defined and is especially a halogen atom or a C₁₋₃alkyl, C₁₋₃alkoxy or –CN group

15 In general in compounds of formula (1) L is preferably a –CH₂– group.

Particularly useful compounds of the invention include each of the compounds described in the Examples hereinafter, and the salts, solvates, hydrates and N-oxides thereof.

20

Compounds according to the invention, including 3,7-dibenzyl-1,7-dihydro-2H-purinone, are potent and selective inhibitors of p38 kinases, including all isoforms and splice variants thereof. More specifically these compounds are inhibitors of p38 α , p38 β and p38 β 2. The ability of the compounds to act in this way may be simply determined by employing tests such as those described in the Examples hereinafter.

25

The compounds of formula (1) and 3,7-dibenzyl-1,7-dihydro-2H-purinone are of use in modulating the activity of p38 kinases and in particular are of use in the prophylaxis and treatment of any p38 kinase mediated diseases or disorders in a human, or other mammal. The invention extends to such a use

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and to the use of the compounds for the manufacture of a medicament for treating such diseases or disorders. Further the invention extends to the administration to a human an effective amount of a p38 inhibitor as herein described for treating any such disease or disorder.

5

Diseases or disorders in which p38 kinase plays a role either directly or via pro-inflammatory cytokines including the cytokines TNF, IL-1, IL-6 and IL-8 include without limitation autoimmune diseases, inflammatory diseases, destructive-bone disorders, proliferative disorders, neurodegenerative disorders, viral diseases, allergies, infectious diseases, heart attacks, angiogenic disorders, reperfusion/ischemia in stroke, vascular hyperplasia, organ hypoxia, cardiac hypertrophy, thrombin-induced platelet aggregation and conditions associated with prostaglandin endoperoxidase synthetase-2 (COX-2).

15

Autoimmune diseases which may be prevented or treated include but are not limited to rheumatoid arthritis, inflammatory bowel disease, ulcerative colitis, Crohn's disease, multiple sclerosis, diabetes, glomerulonephritis, systemic lupus erythematosus, scleroderma, chronic thyroiditis, Grave's disease, hemolytic anemia, autoimmune gastritis, autoimmune neutropenia, thrombocytopenia, chronic active hepatitis, myasthenia gravis, atopic dermatitis, graft vs host disease or psoriasis.

25

Inflammatory diseases which may be prevented or treated include but are not limited to asthma, allergies, respiratory distress syndrome or acute or chronic pancreatitis.

30

Destructive bone disorders which may be prevented or treated include but are not limited to osteoporosis, osteoarthritis and multiple myeloma-related bone disorder.

Proliferative diseases which may be prevented or treated include but are not limited to acute or chronic myelogenous leukemia, Kaposi's sarcoma, metastatic melanoma and multiple myeloma.

- 5 Neurodegenerative diseases which may be prevented or treated include but are not limited to Parkinson's disease, Alzheimer's disease, cerebral ischemias or neurodegenerative disease caused by traumatic injury.

- 10 Viral diseases which may be prevented or treated include but are not limited to acute hepatitis infection (including hepatitis A, hepatitis B and hepatitis C), HIV infection and CMV retinitis.

Infectious diseases which may be prevented or treated include but are not limited to septic shock, sepsis and Shigellosis.

15

- In addition, p38 inhibitors of this invention also exhibit inhibition of expression of inducible pro-inflammatory proteins such as prostaglandin endoperoxidase synthetase-2, otherwise known as cyclooxygenase-2 (COX-2) and are therefore of use in therapy. Pro-inflammatory mediators of the
- 20 cyclooxygenase pathway derived from arachidonic acid are produced by inducible COX-2 enzyme. Regulation of COX-2 would regulate these pro-inflammatory mediators such as prostaglandins, which affect a wide variety of cells and are important and critical inflammatory mediators of a wide variety of disease states and conditions. In particular these inflammatory mediators
- 25 have been implicated in pain, such as in the sensitization of pain receptors, or edema. Accordingly additional p38 mediated conditions which may be prevented or treated include edema, analgesia, fever and pain such as neuromuscular pain, headache, dental pain, arthritis pain and pain caused by cancer.

30

More particularly, as a result of their p38 inhibitory activity, inhibitors according to the invention have utility in the prevention and treatment of diseases associated with cytokine production including but not limited to those diseases associated with TNF, IL-1, IL-6 and IL-8 production.

5

Thus TNF mediated diseases or conditions include for example rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions, sepsis, septic shock syndrome, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoidosis, bone resorption disease, reperfusion injury, graft vs. host reaction, allograft rejections, fever and myalgias due to infection, cachexia secondary to infection, AIDS, ARC or malignancy, keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis, pyresis, viral infections such as HIV, CMV, influenza and herpes; and veterinary viral infections, such as lentivirus infections, including but not limited to equine infectious anemia virus, caprine arthritis virus, visna virus or maedi virus; or retrovirus infections, including feline immunodeficiency virus, bovine immunodeficiency virus or canine immunodeficiency virus.

20 Inhibitors according to the invention may also be used in the treatment of viral infections, where such viruses elicit TNF production *in vivo* or are sensitive to upregulation by TNF. Such viruses include those that produce TNF as a result of infection and those that are sensitive to inhibition, for instance as a result of decreased replication, directly or indirectly by the inhibitors of the invention. Such viruses include, but are not limited to, HIV-1, HIV-2 and HIV-3, Cytomegalovirus (CMV), Influenza, adenovirus and the Herpes group of viruses such as Herpes Zoster and Herpes Simplex.

IL-1 mediated diseases or conditions include for example rheumatoid arthritis, osteoarthritis, psoriatic arthritis, traumatic arthritis, rubella arthritis, inflammatory bowel disease, stroke, endotoxemia and/or toxic shock

syndrome, inflammatory reaction induced by endotoxin, diabetes, pancreatic β -cell disease, Alzheimer's disease, tuberculosis, atherosclerosis, muscle degeneration and cachexia.

5 IL-8 mediated diseases and conditions include for example those characterized by massive neutrophil infiltration such as psoriasis, inflammatory bowel disease, asthma, cardiac, brain and renal reperfusion injury, adult respiratory distress syndrome, thrombosis and glomerulonephritis. The increased IL-8 production associated with each of
10 these diseases is responsible for the chemotaxis of neutrophils into inflammatory sites. This is due to the unique property of IL-8 (in comparison to TNF, IL-1 and IL-6) of promoting neutrophil chemotaxis and activation. Therefore, inhibition of IL-8 production would lead to a direct reduction in neutrophil infiltration.

15

It is also known that both IL-6 and IL-8 are produced during rhinovirus (HRV) infections and contribute to the pathogenesis of the common cold and exacerbation of asthma associated with HRV infection [Turner *et al*, Clin. Infec. Dis., 1997, 26, 840; Grunberg *et al*, Am. J. Crit. Care Med. 1997, 155,
20 1362; Zhu *et al*, J. Clin. Invest. 1996, 97, 421]. It has also been demonstrated *in vitro* that infection of pulmonary epithelial cells (which represent the primary site of infection by HRV) with HRV results in production of IL-6 and IL-8 [Sabauste *et al*, J. Clin. Invest. 1995, 96, 549]. Therefore, p38 inhibitors of the invention may be used for the treatment or prophylaxis of the common
25 cold or respiratory viral infection caused by human rhinovirus infection (HRV), other enteroviruses, coronavirus, influenza virus, parainfluenza virus, respiratory syncytial virus or adenovirus infection.

For the prophylaxis or treatment of a p38 or pro-inflammatory cytokine
30 mediated disease the inhibitors according to the invention may be administered to a human or mammal as pharmaceutical compositions, and

according to a further aspect of the invention we provide a pharmaceutical composition which comprises a compound of formula (1) or 3,7-dibenzyl-3,7 dihydro-2H-purinone together with one or more pharmaceutically acceptable carriers, excipients or diluents.

5

Pharmaceutical compositions according to the invention may take a form suitable for oral, buccal, parenteral, nasal, topical, ophthalmic or rectal administration, or a form suitable for administration by inhalation or insufflation.

10

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets, lozenges or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents, emulsifying agents, non-aqueous vehicles and preservatives. The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

25

Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

30

For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

5 The compounds for formula (1) may be formulated for parenteral administration by injection e.g. by bolus injection or infusion. Formulations for injection may be presented in unit dosage form, e.g. in glass ampoule or multi dose containers, e.g. glass vials. The compositions for injection may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending,
10 stabilising, preserving and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

15 In addition to the formulations described above, the compounds of formula (1) may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation or by intramuscular injection.

20 For nasal administration or administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation for pressurised packs or a nebuliser, with the use of suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas or mixture of gases.

25 The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack or dispensing device may be accompanied by instructions for administration.

30

For topical administration the compounds for use according to the present invention may be conveniently formulated in a suitable ointment containing the active component suspended or dissolved in one or more pharmaceutically acceptable carriers. Particular carriers include, for example,
5 mineral oil, liquid petroleum, propylene glycol, polyoxyethylene, polyoxypropylene, emulsifying wax and water. Alternatively the compounds for use according to the present invention may be formulated in a suitable lotion containing the active component suspended or dissolved in one or more pharmaceutically acceptable carriers. Particular carriers include, for
10 example mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, benzyl alcohol, 2-octyldodecanol and water.

For ophthalmic administration the compounds for use according to the present invention may be conveniently formulated as microionized
15 suspensions in isotonic, pH adjusted sterile saline, either with or without a preservative such as bactericidal or fungicidal agent, for example phenylmercuric nitrate, benzylalkonium chloride or chlorhexidine acetate. Alternatively for ophthalmic administration compounds may be formulated in an ointment such as petrolatum.

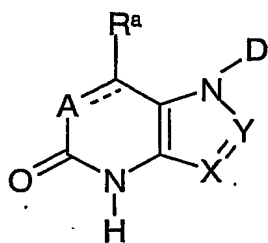
20 For rectal administration the compounds for use according to the present invention may be conveniently formulated as suppositories. These can be prepared by mixing the active component with a suitable non-irritating excipient which is solid at room temperature but liquid at rectal temperature
25 and so will melt in the rectum to release the active component. Such materials include for example cocoa butter, beeswax and polyethylene glycols.

The quantity of a compound of the invention required for the prophylaxis or
30 treatment of a particular condition will vary depending on the compound chosen, and the condition of the patient to be treated. In general, however,

daily dosages may range from around 100ng/kg to 100mg/kg e.g. around 0.01mg/kg to 40mg/kg body weight for oral or buccal administration, from around 10ng/kg to 50mg/kg body weight for parenteral administration and around 0.05mg to around 1000mg e.g. around 0.5mg to around 1000mg for nasal administration or administration by inhalation or insufflation.

The compounds of the invention may be prepared by a number of processes as generally described below and more specifically in the Examples hereinafter. In the following process description, the symbols Ar, Cy¹, Alk¹, n, L¹, L, R^a, A, X and Y when used in the formulae depicted are to be understood to represent those groups described above in relation to formula (1) unless otherwise indicated. In the reactions described below, it may be necessary to protect reactive functional groups, for example hydroxy, amino, thio or carboxy groups, where these are desired in the final product, to avoid their unwanted participation in the reactions. Conventional protecting groups may be used in accordance with standard practice [see, for example, Green, T. W. in "Protective Groups in Organic Synthesis", John Wiley and Sons, 1999]. In some instances, deprotection may be the final step in the synthesis of a compound of formula (1) and the processes according to the invention described hereinafter are to be understood to extend to such removal of protecting groups.

Thus according to a further aspect of the invention a compound of formula (1) in which Cy¹ is as previously defined, but is other than an aromatic or heteroaromatic group when n is zero and L¹ is a covalent bond, may be prepared by alkylation of a compound of formula (2):



(2)

(where D is a hydrogen atom, a group $-LAr$, or a protecting group), with an alkylating agent of formula $Cy^1L^1(Alk^1)_nZ$, where Cy^1 is as just defined and Z is a leaving group such as a halogen atom, e.g. a chlorine, bromine or iodine atom or a sulphonyloxy group such as an alkylsulphonyloxy e.g. trifluoromethylsulphonyloxy or arylsulphonyloxy e.g. phenylsulphonyloxy group.

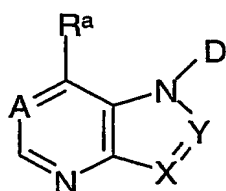
- 10 The reaction may be performed in the presence of a solvent, for example a substituted amide such as dimethylformamide, optionally in the presence of a base, for example an inorganic base such as sodium hydride or potassium carbonate, or an organic base such as an organic amine, e.g. a cyclic amine such as 1,5-diazabicyclo[4.3.0]non-5-ene or a resin bound organic amine
- 15 such as resin bound 2-*tert*-butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine (PS-BEMP), at an elevated temperature, for example 80 to 100°C.

Intermediates of formula (2) may also be used in another process according to the invention to prepare a compound of formula (1) in which n is zero, L is a covalent bond and Cy^1 is an optionally substituted aromatic or heteroaromatic group by the reaction of the intermediate with a boronic acid of formula $Cy^1B(OH)_2$ in which Cy^1 is as just defined. The reaction may be performed in an organic solvent, for example a halogenated hydrocarbon

- 25 such as dichloromethane or dichloroethane in the presence of a copper reagent, for example a copper (II) reagent such as copper (II) acetate, optionally in the presence of an oxidant, for example 2,2,6,6-tetramethyl-1-

piperidinyloxy or pyridine-N-oxide, optionally in the presence of a base, for example an organic amine such as an alkylamine, e.g. triethylamine or an aromatic amine, e.g. pyridine at a temperature from around ambient to the reflux temperature [see for example Chan, D.T. *et al* Tetrahedron Letters, 1998, 2933; Lam, P.Y.S. *et al*, Tetrahedron Letters, 2001, 3415].

Intermediates of formula (2) are either known compounds (see for example Andresen *et al*, *ibid*) or may be prepared in a multi-step process, firstly by oxidation of the corresponding pyridines or pyrimidines of formula (3)



with an oxidising agent such as hydrogen peroxide in the presence of an acid such as acetic acid, at an elevated temperature, for example around 70°C to 80°C, or alternatively by reaction with a peracid such as peracetic acid or m-chloroperoxybenzoic acid in a solvent, such as an ester, e.g. ethyl acetate, a halogenated hydrocarbon e.g. dichloromethane or an alcohol e.g. tert-butanol at a temperature from the ambient temperature to the reflux temperature, to yield the corresponding N-oxide; followed by sequential reaction with an anhydride, for example acetic anhydride, at an elevated temperature, such as the reflux temperature, and then by reaction with an inorganic base, for example a carbonate such as aqueous potassium carbonate in a solvent such as an ether for example a cyclic ether e.g. tetrahydrofuran at around ambient temperature, to yield the desired intermediate of formula (2). Alternatively the N-oxide may be treated with trifluoroacetic anhydride in

dimethylformamide from 0°C to ambient temperature to yield the desired intermediate [see for example Konno et al., Heterocycles (1986) 24, 2169].

Intermediates of formula (3) in which D is a protecting group can be advantageously used in the above reactions to generate a variety of compounds of the invention. Thus for example an Intermediate of formula (3) in which D is a phenylsulphonyl group may be oxidised, converted to the corresponding pyridinone or pyrimidinone of formula (2), and then alkylated or arylated according to the reactions described above. At this point the phenylsulphonyl group can be removed, for example by treatment with a base such as sodium hydroxide in an alcohol such as methanol at ambient temperature. The resulting deprotected intermediate can then be reacted, in another process according to the invention, with a compound ArLZ (where Z is a leaving group as defined above) in the presence of a base and suitable solvent, as described above for the alkylation of Intermediates of formula (2), to yield a desired compound of formula (1).

Where in the processes described above Intermediates of formula (3) and other intermediates such as alkylating agents of formula $Cy^1L^1(Alk^1)_nZ$, and any other intermediates required in the synthesis of compounds of the invention are not available commercially or known in the literature, they may be readily obtained from simpler known compounds by one or more standard synthetic methods employing substitution, oxidation, reduction or cleavage reactions. Particular substitution approaches include conventional alkylation, arylation, heteroarylation, acylation, thioacylation, halogenation, sulphonylation, nitration, formylation and coupling procedures. It will be appreciated that these methods may also be used to obtain or modify other intermediates and in particular compounds of formula (1) where appropriate functional groups exist in these compounds.

30

Thus for example Intermediates of formula (3) where D is a protecting group such as an arylsulphonyl group may be obtained from the corresponding 1H-compounds by reaction with a compound ArSO_2Hal (where Hal is a halogen atom such as a chlorine atom) in the presence of a base such as sodium hydride in a solvent such as dimethylsulfoxide at ambient temperature. Similarly, compounds of the invention and intermediates thereto generally may be obtained by sulphonylation of a compound containing an -OH group by reaction with one of the above alkylating agents but in which Z is replaced by a $-\text{S}(\text{O})\text{Hal}$ or $-\text{SO}_2\text{Hal}$ group in the presence of a base, for example an inorganic base such as sodium hydride in a solvent such as an amide, e.g. a substituted amide such as dimethylformamide at for example ambient temperature.

Compounds of the invention and intermediates thereto where A represents a $-\text{N}(\text{R}^b)-$ or $-\text{C}(\text{R}^b)(\text{R}^c)-$ group may be generated from corresponding compounds of the invention or intermediates thereto where A represents a $-\text{N}=$ or $-\text{C}(\text{R}^b)=$ group by reduction, for instance by catalytic hydrogenation using a metal catalyst such as palladium on charcoal in the presence of hydrogen gas at an elevated pressure in a solvent such as an alcohol, e.g. ethanol optionally at an elevated temperature e.g. between 40°C and 60°C .

Aromatic halogen substituents in the compounds of the invention may be subjected to halogen-metal exchange with a base, for example a lithium base such as n-butyl or t-butyl lithium, optionally at a low temperature, e.g. around -78°C , in a solvent such as tetrahydrofuran and then quenched with an electrophile to introduce a desired substituent. Thus, for example, a formyl group may be introduced by using dimethylformamide as the electrophile, a thiomethyl group may be introduced by using dimethyldisulphide as the electrophile, an alcohol group may be introduced by using an aldehyde as electrophile and an acid may be introduced by using carbon dioxide as

electrophile. Aromatic acids of formula ArCO_2H may also be generated by quenching Grignard reagents of formula ArMgHal with carbon dioxide.

5 Aromatic acids of formula ArCO_2H generated by this method and acid containing compounds in general may be converted to activated derivatives, e.g. acid halides by reaction with a halogenating agent such as a thionyl halide e.g. thionyl chloride, a phosphorous trihalide such as phosphorous trichloride or a phosphorous pentahalide such as phosphorous pentachloride optionally in an inert solvent such as an aromatic hydrocarbon e.g. toluene or
10 a chlorinated hydrocarbon e.g. dichloromethane at a temperature from about 0°C to the reflux temperature, or may be converted into Weinreb amides of formula $\text{ArC}(\text{O})\text{N}(\text{OCH}_3)\text{CH}_3$ by conversion to the acid halide as just described and subsequent reaction with an amine of formula $\text{HN}(\text{OCH}_3)\text{CH}_3$ or a salt thereof, optionally in the presence of a base such as an organic
15 amine, e.g. triethylamine in an inert solvent such as an aromatic hydrocarbon e.g. toluene or a chlorinated hydrocarbon e.g. dichloromethane at a temperature from about 0°C to ambient temperature.

20 Compounds of the invention and intermediates thereto may be prepared by alkylation, arylation or heteroarylation. For example, compounds containing a $-\text{L}^1\text{H}$ group (where L^1 is a linker atom or group) may be treated with an alkylating agent Cy^1Z^2 in which Z^2 is a leaving atom or group such as a halogen atom, e.g. a fluorine, chlorine, bromine or iodine atom or a sulphonyloxy group such as an alkylsulphonyloxy, e.g.
25 trifluoromethylsulphonyloxy or arylsulphonyloxy, e.g. p-toluenesulphonyloxy group.

The reaction may be carried out in the presence of a base such as a carbonate, e.g. caesium or potassium carbonate, an alkoxide, e.g. potassium
30 t-butoxide, or a hydride, e.g. sodium hydride, in a dipolar aprotic solvent such

as an amide, e.g. a substituted amide such as dimethylformamide or an ether, e.g. a cyclic ether such as tetrahydrofuran.

5 In another example, compounds containing a $-L^2H$ group as defined above may be functionalised by acylation or thioacylation, for example by reaction with the alkylating agents just described but in which Z^2 is replaced by a $-C(O)Z^3$, $C(S)Z^3$, $-N(R^2)COZ^3$ or $-N(R^2)C(S)Z^3$ group in which Z^3 is a leaving atom or group as described for Z^2 . The reaction may be performed in the presence of a base, such as a hydride, e.g. sodium hydride or an amine, e.g. triethylamine or N-methylmorpholine, in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane or carbon tetrachloride or an amide, e.g. dimethylformamide, at for example ambient temperature. Alternatively, the acylation may be carried out under the same conditions with an acid (for example one of the alkylating agents described above in which Z^2 is replaced
15 by a $-CO_2H$ group) in the presence of a condensing agent, for example a diimide such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide or N,N'-dicyclohexylcarbodiimide, or a benzotriazole such as [O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium]hexafluorophosphate advantageously in the presence of a catalyst such as a N-hydroxy compound e.g. a N-hydroxytriazole such as 1-hydroxybenzotriazole. Alternatively the acid may
20 be reacted with a chloroformate, for example ethylchloroformate, prior to the desired acylation reaction

25

In another example, compounds containing a $-L^2H$ group as defined above may be coupled with one of the alkylation agents just described but in which Z^2 is replaced by an $-OH$ group in a solvent such as tetrahydrofuran in the presence of a phosphine, e.g. triphenylphosphine and an activator such as diethyl, diisopropyl- or dimethylazodicarboxylate.
30

- Ester groups such as $-\text{CO}_2\text{Alk}^6$ and $-\text{CO}_2\text{R}^4$ in the compound of formula (1) and intermediates thereto may be converted to the corresponding acid $[-\text{CO}_2\text{H}]$ by acid- or base-catalysed hydrolysis depending on the nature of the group Alk^6 or R^4 . Acid- or base-catalysed hydrolysis may be achieved for
- 5 example by treatment with an organic or inorganic acid, e.g. trifluoroacetic acid in an organic solvent e.g. dichloromethane or a mineral acid such as hydrochloric acid in a solvent such as dioxan or an alkali metal hydroxide, e.g. lithium hydroxide in an aqueous alcohol, e.g. aqueous methanol.
- 10 In a further example, $-\text{OR}^6$ [where R^6 represents an alkyl group such as methyl group] in compounds of formula (1) and intermediates thereto may be cleaved to the corresponding alcohol $-\text{OH}$ by reaction with boron tribromide in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane at a low temperature, e.g. around -78°C .
- 15 Alcohol $[-\text{OH}]$ groups may also be obtained by hydrogenation of a corresponding $-\text{OCH}_2\text{R}^{31}$ group (where R^{31} is an aryl group) using a metal catalyst, for example palladium on a support such as carbon in a solvent such as ethanol in the presence of ammonium formate, cyclohexadiene or
- 20 hydrogen, from around ambient to the reflux temperature. In another example, $-\text{OH}$ groups may be generated from the corresponding ester [e.g. $-\text{CO}_2\text{Alk}^6$] or aldehyde $[-\text{CHO}]$ by reduction, using for example a complex metal hydride such as lithium aluminium hydride or sodium borohydride in a solvent such as methanol.
- 25 In another example, alcohol $-\text{OH}$ groups in the compounds may be converted to a corresponding $-\text{OR}^6$ group by coupling with a reagent R^6OH in a solvent such as tetrahydrofuran in the presence of a phosphine, e.g. triphenylphosphine and an activator such as diethyl-, diisopropyl-, or
- 30 dimethylazodicarboxylate.

Aminosulphonylamino [-NHSO₂NH₂] groups in the compounds may be obtained, in another example, by reaction of a corresponding amine [-NH₂] with sulphamide in the presence of an organic base such as pyridine at an elevated temperature, e.g. the reflux temperature.

5

In another example compounds containing a -NHCSR⁷ or -CSNHR⁷ group may be prepared by treating a corresponding compound containing a -NHCOR⁷ or -CONHR⁷ group with a thiation reagent, such as Lawesson's Reagent or P₂S₅, in an anhydrous solvent, for example a cyclic ether such as tetrahydrofuran, at an elevated temperature such as the reflux temperature.

10

In a further example amine (-NH₂) groups may be alkylated using a reductive alkylation process employing an aldehyde and a reducing agent. Suitable reducing agents include borohydrides for example sodium triacetoxyborohydride or sodium cyanoborohydride. The reduction may be carried out in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane, a ketone such as acetone, or an alcohol, e.g. ethanol, where necessary in the presence of an acid such as acetic acid at around ambient temperature. Alternatively, the amine and aldehyde may be initially reacted in a solvent such as an aromatic hydrocarbon e.g. toluene and then subjected to hydrogenation in the presence of a metal catalyst, for example palladium on a support such as carbon, in a solvent such as an alcohol, e.g. ethanol.

15

20

In a further example, amine [-NH₂] groups in compounds of formula (1) and intermediates thereto may be obtained by hydrolysis from a corresponding imide by reaction with hydrazine in a solvent such as an alcohol, e.g. ethanol at ambient temperature.

25

In another example, a nitro [-NO₂] group may be reduced to an amine [-NH₂], for example by catalytic hydrogenation using for example hydrogen in the

30

presence of a metal catalyst, for example palladium on a support such as carbon in a solvent such as an ether, e.g. tetrahydrofuran or an alcohol e.g. methanol, or by chemical reduction using for example a metal, e.g. tin or iron, in the presence of an acid such as hydrochloric acid.

5

In a further example amine ($-\text{CH}_2\text{NH}_2$) groups in compounds of formula (1) and intermediates thereto may be obtained by reduction of nitriles ($-\text{CN}$), for example by catalytic hydrogenation using for example hydrogen in the presence of a metal catalyst, for example palladium on a support such as carbon, or Raney[®] nickel, in a solvent such as an ether e.g. a cyclic ether
10 such as tetrahydrofuran or an alcohol e.g. methanol or ethanol, optionally in the presence of ammonia solution at a temperature from ambient to the reflux temperature, or by chemical reduction using for example a metal hydride e.g. lithium aluminium hydride, in a solvent such as an ether e.g. a cyclic ether
15 such as tetrahydrofuran, at a temperature from 0°C to the reflux temperature.

In another example, sulphur atoms in the compounds, for example when present in a group L^1 or L^2 may be oxidised to the corresponding sulfoxide or sulphone using an oxidising agent such as a peroxy acid, e.g. 3-
20 chloroperoxybenzoic acid, in an inert solvent such as a halogenated hydrocarbon, e.g. dichloromethane, at around ambient temperature.

In a further example N-oxides of compounds of formula (1) may in general be prepared for example by oxidation of the corresponding nitrogen base as
25 described above in relation to the preparation of intermediates of formula (2).

Salts of compounds of formula (1) may be prepared by reaction of compounds of formula (1) with an appropriate base in a suitable solvent or mixture of solvents e.g. an organic solvent such as an ether e.g. diethylether,
30 or an alcohol, e.g. ethanol using conventional procedures.

Where it is desired to obtain a particular enantiomer of a compound of formula (1) this may be produced from a corresponding mixture of enantiomers using any suitable conventional procedure for resolving enantiomers.

5

Thus for example diastereomeric derivatives, e.g. salts, may be produced by reaction of a mixture of enantiomers of formula (1) e.g. a racemate, and an appropriate chiral compound, e.g. a chiral base. The diastereomers may then be separated by any convenient means, for example by crystallisation and
10 the desired enantiomer recovered, e.g. by treatment with an acid in the instance where the diastereomer is a salt.

In another resolution process a racemate of formula (1) may be separated using chiral High Performance Liquid Chromatography. Alternatively, if
15 desired a particular enantiomer may be obtained by using an appropriate chiral intermediate in one of the processes described above. Alternatively, a particular enantiomer may be obtained by performing an enantiomer specific enzymatic biotransformation e.g. an ester hydrolysis using an esterase and then purifying only the enantiomerically pure hydrolysed acid from the
20 unreacted ester antipode.

Chromatography, recrystallisation and other conventional separation procedures may also be used with intermediates or final products where it is desired to obtain a particular geometric isomer of the invention.

25

The following Examples illustrate the invention. All temperatures are in °C. The following abbreviations are used:

EtOAc - ethyl acetate; MeOH - methanol;
DCM - dichloromethane; EtOH - ethanol; Pyr - pyridine;
30 DMSO - dimethylsulphoxide; Me - methyl;
THF - tetrahydrofuran; h - hour; MCPBA - 3-chloroperoxybenzoic acid;

r.t. – room temperature; DMF - N,N-dimethylformamide;

All NMRs were obtained either at 300MHz or 400MHz.

5 Compounds were named with the aid of either Beilstein Autonom supplied by MDL Information Systems GmbH, Theodor-Heuss-Allee 108, D-60486 Frankfurt, Germany or ACD Labs Name (v.5.0) supplied by Avanced Chemical Development, Toronto, Canada.

10 LCMS retention times (RT) quoted were generated on a Hewlett Packard 1100 LC/MS using the following following method: Phenomenex Luna 3 μ C₁₈(2) 50x4.6mm column; mobile phase A = 0.1% formic acid in water; mobile phase B = 0.1% formic acid in MeCN; flow rate of 0.9mLmin⁻¹, column temperature 40°C.

15

Gradient:-	Time	%B
	Initial	5
	2.00	95
	3.00	95
	5.0	5
	5.5	end

20

Intermediate 1

1-Benzenesulfonyl-1H-pyrrolo[3,2-b]pyridine

25 Sodium hydride (203mg, 5.08mmol) was washed twice with hexane, and the residue suspended in DMSO (5mL). 1H-Pyrrolo[3,2-b]pyridine (500mg, 4.24mmol) was added and the reaction stirred for 15 minutes. Benzenesulphonyl chloride (749mg, 4.42mmol) was added rapidly and the reaction stirred for thirty minutes. After quenching with water the product was

30 extracted into EtOAc, dried over sodium sulphate and concentrated in vacuo.

Chromatography (EtOAc–silica) yielded the title compound as a white crystalline solid (903mg).

δ H (DMSO) 8.48 (1H, dd, J 0.8, 3.8Hz), 8.31 (1H, m), 8.15 (1H, d, J 3.8Hz), 8.04 (2H, m), 7.72 (1H, m), 7.61 (2H, m), 7.36 (1H, dd, J 4.7, 8.4Hz), 6.98 (1H, dd, J 0.8, 3.8Hz).

LCMS (ES⁺) RT 3.056 minutes, 259 (M+H)⁺.

Intermediate 2

1-Benzenesulfonyl-1H-pyrrolo[3,2-b]pyridine 4-oxide

10 Intermediate 1 (903mg, 3.5mmol) was dissolved in EtOAc (6mL) and treated with MCPBA (903mg, 5.25mmol). After stirring for 24h the reaction mixture was washed with saturated sodium hydrogen carbonate solution, dried over magnesium sulphate and concentrated in vacuo. Chromatography (EtOAc–silica) yielded the title compound as a white foam (860mg).

15 δ H (DMSO) 8.24 (1H, d, J 6.6Hz), 8.15 (3H, m), 7.9(1H, d, J 8.3Hz), 7.76 (1H, m), 7.68 (2H, m), 7.35 (1H, dd, J 6.3, 8.5Hz), 7.1 (1H, dd, J 0.8, 3.8Hz). HPLC RT 2.774 minutes.

Intermediate 3

1-Benzenesulfonyl-1,4-dihydro-pyrrolo[3,2-b]pyridin-5-one

Intermediate 2 (0.86g, 3.1mmol) was dissolved in DMF (8mL) and treated with trifluoroacetic anhydride (6.6g, 31.4mmol) at r.t. and stirred for 4 days. The reaction mixture was concentrated in vacuo, redissolved in EtOH, concentrated again then partitioned between water and toluene. The organic layer was dried over magnesium sulphate and concentrated to yield the title compound as a beige solid (657mg).

25 δ H (DMSO) 8.20(1H, d, J 8.6Hz), 8.11(2H, m), 7.94(1H, d, J 3.7Hz), 7.88(1H, d, J 8.4Hz), 7.78(2H, m), 6.58(1H, d, J 3.6Hz), 6.45(1H, d, J 9.6Hz). LCMS (ES⁺) RT 2.775minutes 275(M+H)⁺.

Intermediate 4

1-Benzenesulfonyl-4-phenyl-1,4-dihydro-pyrrolo[3,2-b]pyridin-5-one

Intermediate 3 (300mg, 1.09mmol) was combined with phenylboronic acid (343mg, 2.19mmol), copper (II) acetate (437mg, 2.19mmol), and pyridine (319mg, 0.41mL 3.28mmol) in DCM. The reaction was stirred at r. t. for 24h.

5 then diluted with further DCM, washed with water, separated, the organic layer dried and concentrated in vacuo. Column chromatography (EtOAc-silica) yielded the title compound (150mg).

δ (DMSO) 7.95(1H, d, J 9.8Hz), 7.90(2H, d, J 8.5Hz), 7.60(2H, m), 7.53(2H, m), 7.35(3H, m), 7.16(2H, d, J 1.7, 8.3Hz), 6.23(1H, d, J 9.8Hz), 5.70(1H, dd, J 0.6, 3.7Hz).

10 LCMS (ES⁺) RT 3.312minutes 351(M+H)⁺.

Intermediate 5

4-phenyl-1,4-dihydro-pyrrolo[3,2-b]pyridin-5-one

15 Intermediate 4 (1.5g, 4.3mmol) in MeOH (10mL) was treated with 2M sodium hydroxide (5mL) and stirred at r.t. for 2h. The organic phase was removed under reduced pressure, the residue neutralised with 2M hydrochloric acid then extracted into DCM dried over magnesium sulphate and concentrated in vacuo to yield the title compound (765mg).

20 δ (CDCl₃) 9.30(1H, brs), 7.44(3H, m), 7.36(3H, m), 6.84(1H, t, J 3.0Hz), 6.37(1H, d, J 9.4Hz), 5.59(1H, t, J 2.3Hz).

Intermediate 6

1-Benzenesulfonyl-4-(4-methoxy-phenyl)-1,4-dihydro-pyrrolo[3,2-b]pyridin-5-one

25 The title compound was prepared in a similar manner to Intermediate 4 from Intermediate 3 (300mg, 1.09mmol) and 4-methoxyphenylboronic acid (333mg, 2.19mmol):

30 δ (DMSO) 8.12(1H, d, J 9.8Hz), 8.06(2H, m), 7.75(4H, m), 7.25(2H, dd, J 2.2, 9.0Hz), 7.05(2H, dd, J 2.2, 9.0Hz), 6.40(1H, d, J 9.8Hz), 5.91(1H, dd, J 0.5, 3.6Hz), 3.81(3H, s).

LCMS (ES⁺) RT 3.309minutes 381(M+H)⁺.

Intermediate 7

4-(4-Methoxy-phenyl)-1,4-dihydro-pyrrolo[3,2-b]pyridin-5-one

- 5 The title compound (30mg) was prepared in a similar manner to Intermediate 5 from Intermediate 6 (25mg, 0.066mmol):

δ (CDCl₃) 9.04(1H, brs), 7.46(1H, dd, J 0.5, 9.3Hz), 7.25(2H, m), 6.96(2H, m), 6.89(1H, apparent t, J 2.9Hz), 6.38(1H, d, J 9.3Hz), 5.63(1H, apparent t, J 2.3Hz), 3.78(3H, s).

- 10 HPLC RT 2.608minutes

Intermediate 8

Phenyl-pyrrolo[3,2-b]pyridin-1-yl-methanone

- 15 The title compound was prepared as a yellow crystalline solid (429mg) in a similar manner to Intermediate 1 using benzoyl chloride (596mg, 4.42mmol) in place of benzenesulphonyl chloride:

δ (DMSO) 8.60(1H, m), 8.50(1H, m), 7.79(2H, m), 7.74(2H, m), 7.63(2H, m), 7.39(1H, dd, J 4.7, 8.3Hz), 6.86(1H, dd, J 0.6, 3.9Hz).

LCMS (ES⁺) RT 2.622minutes 223(M+H)⁺.

20

Intermediate 9

(4-Oxy-pyrrolo[3,2-b]pyridin-1-yl)-phenyl-methanone

The title compound was prepared as a white foam (403mg) in a similar manner to Intermediate 2 using Intermediate 8 (429mg, 1.93mmol):

- 25 δ (DMSO) 8.28(1H, d, J 7.7Hz), 8.10(1H, d, J 8.8Hz), 7.81(2H, d, J 7.7Hz), 7.74(1H, m), 7.67(3H, m), 7.38(1H, dd, J 6.4, 8.5Hz), 6.98(1H, m).

LCMS (ES⁺) RT 2.612minutes 239(M+H)⁺.

Intermediate 10

- 30 **1-Benzoyl-1,4-dihydro-pyrrolo[3,2-b]pyridin-5-one**

The title compound was prepared as a white crystalline solid (903mg) in a similar manner to Intermediate 3 using Intermediate 9 (400mg, 1.68mmol):
 δ (DMSO) 8.17(1H, d, J 9.9Hz), 7.72(2H, m), 7.66(1H, d, J 8.3Hz), 7.58(2H, m), 7.29(1H, m), 6.31(1H, m), 6.24(1H, d, J 9.9Hz).

5

Example 1

1-Benzyl-4-phenyl-1,4-dihydro-pyrrolo[3,2-b]pyridin-5-one

Intermediate 5 (140mg, 0.67mmol) was added to sodium hydride (53mg, 1.33mmol) suspended in THF (2mL). Benzyl chloride (125mg, 0.73mmol) was added and the reaction stirred at r.t. for 30 minutes. The reaction mixture was concentrated in vacuo and chromatographed (gradient elution DCM-EtOAc-silica), to yield the title compound (168mg).

δ (CDCl₃) 7.56(2H, m), 7.46(4H, m), 7.38(3H, m), 7.17(2H, m), 6.92(1H, d, J 3.0Hz), 6.44(1H, d, J 9.5Hz), 5.68(1H, d, J 2.7Hz), 5.25(2H, s).

15 LCMS (ES⁺) RT 3.241minutes 301(M+H)⁺.

The compounds of Examples 2 – 5 were made by a similar procedure to the compound of Example 1, using Intermediate 5 and the appropriate substituted benzyl chloride:

20

Example 2

1-(3-Chloro-benzyl)-4-phenyl-1,4-dihydro-pyrrolo[3,2-b]pyridin-5-one

δ (CDCl₃) 7.49(2H, m), 7.36(4H, m), 7.23(2H, m), 7.06(1H, d, J 0.7Hz), 6.94(1H, m), 6.84(1H, d, J 3.0Hz), 6.36(1H, d, J 9.6Hz), 5.61(1H, dd, J 0.6, 3Hz), 5.12(2H, s).

25

LCMS (ES⁺) RT 3.418minutes 335(M+H)⁺.

Example 3

1-(4-Fluoro-benzyl)-4-phenyl-1,4-dihydro-pyrrolo[3,2-b]pyridin-5-one

δ (CDCl₃) 7.48(2H, m), 7.37(4H, m), 7.09(2H, m), 7.00(2H, m), 6.83(1H, d, J 3.0Hz), 6.37(1H, d, J 9.5Hz), 5.61(1H, d, J 3.0Hz), 5.14(2H, s).
LCMS (ES⁺) RT 3.252minutes 319(M+H)⁺.

5 **Example 4**

1-(2,6-Dichloro-benzyl)-4-phenyl-1,4-dihydro-pyrrolo[3,2-b]pyridin-5-one

δ (CDCl₃) 7.61(1H, d, J 9.5Hz), 7.43(2H, m), 7.32(5H, m), 7.21(1H, m),
6.65(1H, d, J 3.1Hz), 6.40(1H, d, J 9.5Hz), 5.49(1H, d, J 3.1Hz), 5.38(2H, s).
LCMS (ES⁺) RT 3.552minutes 369(M+H)⁺.

10

Example 5

1-(3-Methoxy-benzyl)-4-phenyl-1,4-dihydro-pyrrolo[3,2-b]pyridin-5-one

δ (CDCl₃) 7.46(2H, m), 7.36(4H, m), 7.20(1H, m), 6.82(1H, m), 6.66(1H, d, J 7.6Hz), 6.60(1H, s), 6.34(1H, d, J 9.5Hz), 5.58(1H, d, J 3.0Hz), 5.11(2H, s),
3.71(3H, s).

15

LCMS (ES⁺) RT 3.239minutes 331(M+H)⁺.

Example 7

1-Benzyl-4-(4-methoxy-phenyl)-1,4-dihydro-pyrrolo[3,2-b]pyridin-5-one

20 The title compound (9mg) was prepared in a similar manner to the compound of Example 1 from Intermediate 7 (30mg, 0.125mmol) and benzyl chloride (18mg, 0.14mmol):

δ (CDCl₃) 7.34(1H, d, J 7.7Hz), 7.28(5H, m), 7.10(2H, d, J 4.4Hz), 6.98(2H, d, J 6.6Hz), 6.82(1H, d, J 2.2Hz), 6.33(1H, d, J 7.7Hz), 5.60(1H, d, J 2.2Hz),
5.15(2H, s), 3.80(3H, s).

25

LCMS (ES⁺) RT 3.304minutes 331(M+H)⁺.

30 **Example 8**

1-Benzoyl-4-phenyl-1,4-dihydro-pyrrolo[3,2-b]pyridin-5-one

The title compound (146mg) was prepared in a similar manner to Intermediate 4, from Intermediate 10:

5 δ (DMSO) 8.32(1H, d, J 9.8Hz), 7.75(3H, m), 7.59(5H, m), 7.40(2H, dd, J 1.5, 8.4Hz), 7.30(1H, d, J 3.7Hz), 6.43(1H, d, J 9.8Hz), 5.81(1H, dd, J 0.3, 4.1Hz).
LCMS (ES⁺) RT 3.299minutes 315(M+H)⁺.

The following assays and animal models can be used to demonstrate the potency and selectivity of the compounds according to the invention. In each
10 assay an IC₅₀ value was determined for each test compound and represents the concentration of compound necessary to achieve 50% inhibition.

Preparation of activated human p38 α for inhibitor assays.

15 **Purification of human p38 α**

Human p38 α , incorporating an N-terminal (His)₆ tag, was expressed in baculovirus-infected High-Five™ cells (Invitrogen) according to the manufacturers instructions. The cells were harvested 72h post-infection and lysed in phosphate buffered saline (PBS) containing 1% (w/v) β -
20 octylglucoside and Complete, EDTA-free™ protease inhibitors (Roche Molecular Biochemicals). The lysate was centrifuged at 35000xg for 30min at 4oC and the supernatant applied to a NiNTA™ column (Qiagen). Bound protein was eluted by 150mM imidazole in PBS (after a wash with 15mM imidazole in PBS) and directly applied to a HiTrap Q™ column (AP Biotech).
25 Bound protein was eluted using a 20 column volume, 0 to 1M NaCl gradient. Fractions containing (His)₆-p38 were aliquotted and stored at -70° prior to their activation.

Preparation of GST-MKK6EE-containing lysates

30 E. coli (BL21 pLysS) expressing the constitutively activated form of human MKK6 fused with an N-terminal glutathione-S-transferase tag (GST-

MKK6EE) were harvested by centrifugation and frozen at -70° . Cells were lysed by resuspension in 1/10th the culture volume of PBS containing Complete, EDTA-free™ protease inhibitors followed by sonication on ice for 4x15 sec. Cell debris was removed by centrifugation at 35,000xg and the resultant supernatant stored in aliquots at -70° .

Activation of (His)6-p38

0.45mL of purified (His)6-p38 was incubated with 50μL of the GST-MKK6EE-containing lysate for 30min at 23° in the presence of 1mM β -glycerophosphate, 10mM $MgCl_2$ and 9mM ATP. The extent of activation was monitored by mass spectrometric detection of the doubly-phosphorylated form of (His)6-p38, which routinely comprised greater than 90% of the final (His)6-p38 preparation. The activated (His)6-p38 was then diluted x10 in PBS and repurified using the method described above. The concentration of purified, activated (His)6-p38 was measured by UV absorbance at 280nm using $A_{280}, 0.1\% = 1.2$ and the preparation stored in aliquots at -70° prior to its use in inhibitor assays.

p38 Inhibition Assays

20 Inhibition of phosphorylation of biotinylated myelin basic protein (MBP)

The inhibition of p38 catalysed phosphorylation of biotinylated MBP is measured using a DELFIA based format. The assay was performed in a buffer comprising, 20mM HEPES (pH 7.4), 5mM $MgCl_2$ and 3mM DTT. For a typical IC_{50} determination, biotinylated MBP (2.5μM) was incubated at room temperature in a streptavidin-coated microtitre plate together with activated gst-p38 (10nM) and ATP (1μM) in the presence of a range of inhibitor concentrations (final concentration of DMSO is 2 percent). After fifteen minutes the reaction was terminated by the addition of EDTA (75mM). The microtitre plate was then washed with Tris buffered saline (TBS), prior to the addition of 100μl of anti-phospho MBP antibody (mouse) together with europium-labeled anti-mouse IgG antibody. After one hour at room

temperature the plate was again washed in TBS followed by the addition of Enhancement solution (PerkinElmer Wallac). Fluorescence measurements were performed after a further fifteen minutes at room temperature. IC50 values are determined from the plot of Log₁₀ inhibitor concentration (x-axis) versus percentage inhibition of the fluorescence generated by a control sample in the absence of inhibitor (y-axis).

Purification of human Peripheral Blood Mononuclear Cells

Peripheral blood mononuclear cells (PBMC) were isolated from normal healthy volunteers. Whole blood was taken by venous puncture using heparinised vacutainers (Becton Dickinson), diluted 1 in 4 in RPMI 1640 (Gibco, UK) and centrifuged at 400g for 35 min over a Ficoll-paque gradient (Amersham-Pharmacia Biotech, UK). Cells at the interface were removed and washed once followed by a low speed spin (250g) to remove platelets. Cells were then resuspended in DMEM containing 10% FCS, penicillin 100 units ml⁻¹, streptomycin 50µg ml⁻¹ and glutamine 2mM (Gibco, UK).

Inhibitor dilutions

Inhibitor stocks (20mM) were kept as a frozen solution (-20°C) in DMSO. Serial dilutions of inhibitors were performed in DMSO as 250-times concentrated stocks. Inhibitors were diluted 1 in 250 into tissue culture media, prewarmed to 37°C and transferred to plates containing PBMC. PBMC and inhibitors were incubated together for 30 mins prior to addition of LPS. Inhibitors used in whole blood assays were prepared according to a different regime. Using the same stock solution serial dilutions of inhibitors were performed in DMSO. Inhibitors were then diluted 1 in 500 straight into whole blood in a volume of 1µL. Inhibitor was incubated with whole blood for 30 mins prior to the addition of LPS.

LPS stimulation of PBMC

PBMC were resuspended at a density of 2×10^5 cells/well in flat bottomed 96 well tissue culture treated plates. After the addition of inhibitor cells were stimulated with an optimal dose of LPS (*E coli* strain B5:055, Sigma, at a final concentration of $1 \mu\text{g ml}^{-1}$) and incubated at 37°C in 5% CO_2 /95% air for 18 hours. TNF- α levels were measured from cell free supernatants by sandwich ELISA (BioSource #CHC1751).

LPS stimulation of whole blood

Whole blood was taken by venous puncture using heparinised vacutainers (Becton Dickinson), and 500 μl of blood aliquoted into each well of a 24 well tissue culture treated plate. After the addition of inhibitor cells were stimulated with an optimal dose of LPS (*E coli* strain B5:055, Sigma, at a final concentration of $1 \mu\text{g ml}^{-1}$) and incubated at 37°C without CO_2 for 18 hours. TNF- α levels were measured from cell free supernatants by sandwich ELISA (BioSource #CHC1751).

Rat LPS induced TNF release

Male Lewis rats (180-200g) are anaesthetised with Isofluror and injected i.v. with LPS* in a volume of 0.5ml sterile saline. After 90minutes blood is collected into EDTA tubes for preparation of plasma samples. Plasma is stored at -70°C prior to assay for TNF α by commercial ELISA.

Rat CIA

Female Lewis rats (180-200g) are anaesthetised with Isofluror and immunised i.d. at the base of the tail with 2x100 μl of emulsion containing 4mg/ml bovine collagen II in 0.01M acetic acid and Freund's Incomplete Adjuvant at a ratio of 1:1. A polyarthritis develops with onset from about 13 days post sensitisation. The disease is mainly confined to the ankles and is quantified by plethysmometry. Results are expressed as change in paw volume over time.

In the p38 inhibitor assays described above compounds of the invention have IC_{50} values of around $2\mu M$ and below. The compounds of the invention are clearly potent inhibitors of p38 kinase, especially p38 α kinase.

PCT Application
GB0304214

